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Including ALLERGY ABSTRACTS

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The Journal of Allergy

VOL. 27 NOVEMBER, 1956 NO. 6

Original Articles

BLOOD PROTEIN ABNORMALITIES IN ASTHMATIC CHILDREN

HAROLD S. TUFT, M.D., DENVER, COLO.

THE study of gamma globulin levels in children has become more widespread since the discovery of a deficiency state known as agammaglobulinemia.[1] The development and availability of paper electrophoresis apparatus which is more adaptable for clinical laboratory use than the free electrophoresis equipment of the Tiselius[2] type have added impetus to research in this field.

The outstanding clinical feature of agammaglobulinemia is increased susceptibility to infection,[3] particularly of the respiratory tract.[3, 4] Cases reported[1, 3-8] so far have not demonstrated asthma associated with these infections. The asthmatic child also is often susceptible to respiratory infection but the infection in this group is associated very frequently with asthma. The study to follow is a result of the consideration of this disparity and is a portion of a larger study of the etiology of intractability in asthma of childhood.

Cooke and associates[9] performed electrophoretic analysis of the blood of asthmatic patients by the Tiselius method as a part of a study of the mechanism of cortisone effect. Reversion of previously elevated gamma globulin to normal under the influence of cortisone was demonstrated. Their group included only two patients in the age group available for this study. Application of the paper technique to a larger series of children in this age group and the effect of steroid medication on electrophoretic protein values appeared to be a worth-while extension of the original protocol.

Thus, this article comprises a report on the results of serum electrophoresis performed on asthmatic children, aged 5 to 16 years, who were admitted as intractable cases to the Jewish National Home for Asthmatic Children.

Electrophoresis was performed by the paper technique. One hundredth (0.01) milliliter of the serum to be tested was applied to a strip suspended in barbital buffer in a Williams cell (Spinco).[10] Current was applied by means

From the Jewish National Home for Asthmatic Children, Denver, Colorado.

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of a constant output rectifier for sixteen hours. The drying and staining techniques are critical parts of the process; therefore, the precise standards proposed by Durrum and co-workers[11] were used in this study. The stained strips were scanned by means of a Spinco Analytrol, which is a combined scanner and integrator. Gram values for each fraction were obtained by multiplying the percentage found in the scanning procedure by the total protein determined by the biuret[12] method.

Reproducibility is a subject of much discussion in regard to the clinical significance of recorded results. Durrum[11] believes that standardized dyeing and scanning techniques will minimize the inherent errors in the method. Jencks, Letton and Durrum[13] studied reproducibility by the standardized method and showed that the standard deviation for the same serum run forty times over a period of two weeks was statistically acceptable in all fractions. Confirmation of these findings was sought and was obtained as long as the method was closely followed throughout. Duplicate strips were run for each serum tested and the values for each case were obtained by averaging the percentages.

Because of reproducibility problems, determination of the normal pattern for each laboratory is highly recommended.[14] Accordingly, thirty-five determinations on the sera of nineteen healthy normal children known to be free of asthma and allergy were performed. This group constitutes the normal group for this study, labeled *N*.

Paper electrophoresis was applied to the serum of a total of 126 asthmatic patients. All of these children had severe, perennial asthma and were subject to repeated respiratory infections followed by asthma prior to admission to the Home. One hundred twenty-one patients comprised the group for analysis of data on childhood asthma unmodified by steroid hormones. An additional five patients who were tested only when on steroid maintenance dosage and nine of the general group who were tested both while on and off this medication comprised the steroid-treated group, labeled *S*.

A clinical classification of the untreated group which considered only the time interval from the last asthmatic attack to the drawing of blood for the panel was devised. This interval was arbitrarily set at within seven days (Group A), eight to thirty-one days (Group B), and more than thirty-one days (Group C). The patients in Group A were the most chronic of the entire series. Those in Group B were having asthma only occasionally and their asthma was of the acute recurrent type. Those in Group C comprised the recovered patients, patients whose asthma had subsided upon admission to the Home and had not recurred.

The range, mean, and standard deviation for each electrophoretic fraction in relation to the clinical categories are shown in Table I. From inspection of the table, one notes much overlapping of the range of figures in each category but the means exhibit changes which appear to merit further statistical analysis. For example, the means of albumin fraction in the aggregate asthma group, as well as in the individual asthmatic groups, are lower than the mean of the nor-

mal group, but the albumin mean in the steroid group is somewhat higher than in the asthmatic group but lower than in the normal group. Variations from the mean of the normal group appear also in alpha$_1$, alpha$_2$, and gamma globulin fractions under almost all the clinical groups. Beta globulin means appear to be relatively constant throughout the clinical groups.

TABLE I. RANGE, MEAN, AND STANDARD DEVIATION OF PAPER ELECTROPHORETIC VALUES IN GRAMS PER CENT

		NORMAL	TOTAL ABC	A	B	C	S
Albumin	No. Cases	35	121	44	38	39	14
	Range	3.54-4.74	2.34-4.66	2.82-4.66	2.46-4.36	2.34-4.15	3.06-4.34
	Mean	4.22	3.44	3.46	3.39	3.45	3.64
	S. D.	0.31	0.38	0.38	0.42	0.36	0.43
Alpha$_1$ globulin	No. Cases	35	121	44	38	39	14
	Range	0.06-0.40	0.07-0.51	0.08-0.50	0.15-0.51	0.07-0.51	0.15-0.60
	Mean	0.24	0.27	0.28	0.29	0.24	0.34
	S. D.	0.08	0.08	0.08	0.08	0.09	0.13
Alpha$_2$ globulin	No. Cases	35	108	39	34	35	13
	Range	0.42-0.90	0.31-1.13	0.31-1.11	0.40-1.13	0.38-0.99	0.37-1.05
	Mean	0.61	0.73	0.73	0.77	0.68	0.74
	S. D.	0.11	0.16	0.17	0.16	0.15	0.17
Beta globulin	No. Cases	35	108	39	35	35	13
	Range	0.51-1.13	0.51-1.38	0.51-1.38	0.58-1.15	0.51-0.97	0.57-1.06
	Mean	0.76	0.78	0.80	0.81	0.73	0.81
	S. D.	0.14	0.16	0.19	0.15	0.12	0.18
Gamma globulin	No. Cases	35	121	44	38	39	14
	Range	0.45-1.19	0.67-3.00	0.67-2.00	0.72-2.26	0.81-3.00	0.80-1.48
	Mean	0.86	1.23	1.16	1.26	1.29	1.09
	S. D.	0.22	0.36	0.30	0.40	0.36	0.21

The first step in the determination of statistical significance was the arrangement of the data into two separate experiments. These were a comparison of the three asthmatic groups (A, B, and C) with the normal group and a comparison of the total asthmatic group with both the steroid and normal groups. Analysis of variance was applied to both experiments. The F figure obtained indicated that beta globulin merited no further consideration in either experiment. However, the remainder of the F values indicated the necessity of further analysis to discover the degree of the significance of the observed difference.

Accordingly, the t test was used to compare the fraction values of the individual asthmatic groups to the normal group and to each other, as well as to compare the total asthmatic group to the steroid group and to the normal group. The t numbers are shown in Table II. Those which are marked with an asterisk are significant at the 0.01 level of confidence.

This table showed significant variation from normal for albumin, alpha$_2$ globulin, and gamma globulin of the aggregate asthmatic group. Reference to the previous table showed that the changes were decreased albumin and elevated alpha$_2$ and gamma globulin. Variations of significance were noted in the individual asthma groups when compared to normal. The A group, or the most chronic asthmatic group, showed significant variations in all except the alpha$_1$ and beta globulin, but the B group was significantly different in all fractions

except beta globulin. The C group was different only in albumin and gamma globulin, alpha$_1$ and alpha$_2$ approaching normal as pointed out by t values below 2.61, the 0.01 level of confidence. The individual asthma groups exhibited no significant differences from each other in any fraction. However, the t values indicate a tendency of the change in the C, or recovered, group to be only lowered albumin and elevated gamma globulin, whereas the changes in the A and B groups involve the alpha$_1$ and alpha$_2$ globulins as well. This tendency suggests that elevated gamma globulin alone is responsible for the evident reduction in the electrophoretic A/G ratio of a recovered asthmatic population.

TABLE II. T SCORES FOR COMPARISON OF CLINICAL GROUPS

FRACTION	TOTAL ABC/N	A/B	A/C	B/C	A/N	B/N	C/N	TOTAL ABC/S	S/N
Albumin	3.44 *	0.87	0.11	0.81	9.03 *	9.57 *	8.84 *	0.61	1.55 *
Alpha$_1$	2.04 *	0.56	1.97	2.54	2.39 *	2.84 *	0.37	2.64	3.63 *
Alpha$_2$	4.03 *	1.14	1.43	2.49	3.58 *	4.57 *	2.09 *	0.38 *	2.75
Gamma	5.85	1.35	1.79	0.41	3.87	5.04	5.73	4.76	2.21

2.61 significant at 0.01 level.

The effect of steroid medication on electrophoretic fraction values of asthmatic patients was also demonstrated by this table. Significant differences were found in the alpha$_1$, which was increased, and gamma globulin, which was decreased. Variation in albumin, which was lowered, as compared to normal and alpha$_2$, which were increased, was not significant. The steroid-to-normal comparison shows that alpha$_1$ and alpha$_2$ values are significantly different from normal but albumin and gamma globulin are not. It appears that steroids increased albumin toward normal, increased alpha$_1$ had no effect on alpha$_2$, which is elevated in the aggregate asthmatic group, and decreased gamma globulin toward normal.

Fewer numbers of alpha$_2$ and beta globulin fractions were available for study because of an unusual electrophoretic pattern in thirteen cases. Fig. 1 shows a normal pattern of separation on a stained strip and the resultant curve produced by the photoelectric scanner. Fig. 2 shows the type of faulty migration encountered in this unusual group. There is an extra fraction in the alpha$_2$ beta area. Since there were no criteria upon which to base a selection of alpha$_2$ and beta from the three fractions presented, these areas were not measured and therefore were not included in the data.

The results of the paper electrophoresis procedure on sera of asthmatic children confirms the findings of Cooke and associates[9] with regard to gamma globulin. Alpha$_2$ globulin elevation found in this series was also noted in their work, but increased alpha$_1$ globulin, which they reported, was not noted in our group. The combination of lowered albumin and elevated alpha$_2$ and gamma globulin has been found in cases of lupus erythematosis.[15] As noted by Cooke and coworkers,[9] this may be additional evidence relating chronic asthma, and especially chronic intractable asthma, to the so-called collagen diseases.

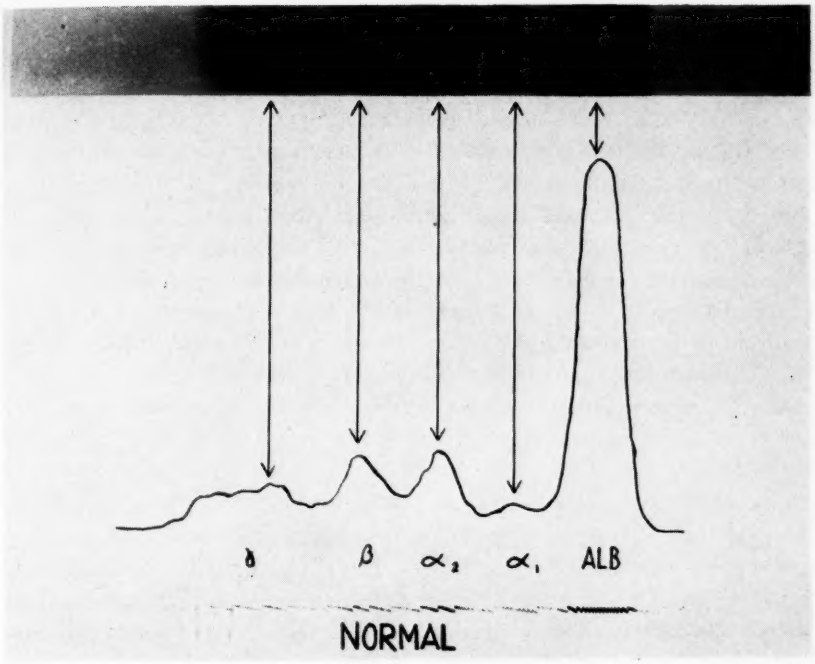

Fig. 1.—Normal paper electrophoretic pattern.

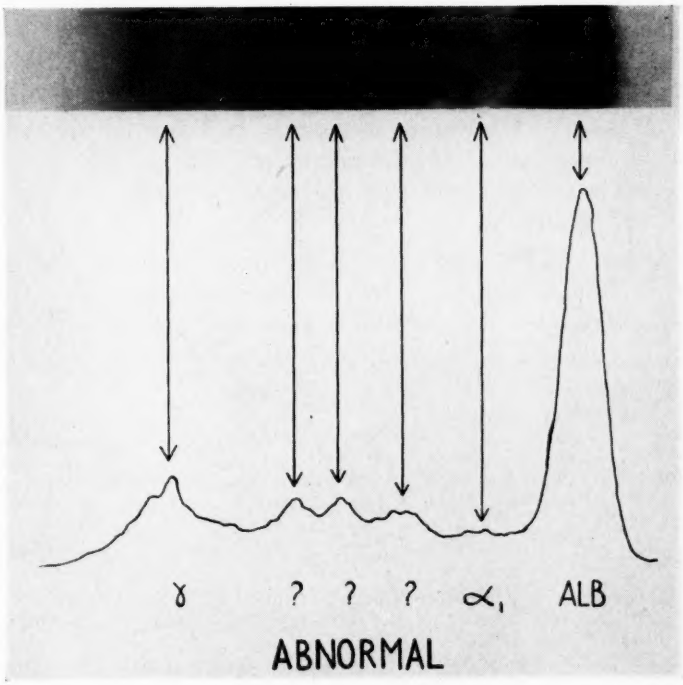

Fig. 2.—Abnormal pattern encountered in thirteen cases showing an extra fraction in the alpha$_2$ beta area.

No case of agammaglobulinemia was found in this study, despite the fact that the history of all patients showed a distinct susceptibility to repeated respiratory infections. Although the incidence of agammaglobulinemia in this age group is small, this result, added to those of Bowen[16] and Cooke and associates,[9] furthers the hypothesis that asthma and agammaglobulinemia do not exist together in the same patient.

Since the patients used in this study have had asthma for relatively long periods of time before admission to the Home, there has been no opportunity to study early cases. An explanation for increased gamma globulin in the late cases may be found in an electrophoretic study at the onset of the disease and at intervals as the disease develops. The statistical validity of the comparisons presented above serves to differentiate groups of cases rather than individual patients. Further study of these children during their stay in the Home is necessary to appraise the significance of the protein abnormalities in the individual child.

Since gamma globulin was found to be present in at least normal amounts in all cases, the parenteral administration of this agent on quantitative grounds alone would seem unnecessary. However, hypergammaglobulinemia was demonstrated in Group C, the group studied at least thirty-one days after asthma. Increased amounts of gamma globulin at least accompany the recovery phase. One may postulate that such increases are necessary for recovery and thus provide a basis for injection of this protein. Proof of the postulate may serve to substantiate the excellent clinical results of Bowen[16] with injected gamma globulin in a group of seventy-five patients with winter asthma.

SUMMARY AND CONCLUSIONS

1. Serum paper electrophoresis performed on 121 asthmatic children showed lowered albumin and elevated alpha$_2$ and gamma globulin. Patients whose asthma had not occurred for at least thirty-one days showed only the albumin and gamma globulin change.

2. The effect of steroid on the electrophoretic pattern was to increase albumin, increase alpha$_1$ globulin, exert no effect on previously elevated alpha$_2$ globulin, and decrease gamma globulin levels toward normal.

3. Thirteen cases of an unusual electrophoretic fraction in the alpha$_2$ beta area were encountered.

The author acknowledges with gratitude the assistance of Drs. Lili Fleck and K. H. Desai, Fellows in Pediatric Allergy, Jewish National Home for Asthmatic Children, Denver, Colorado, in the preparation of the clinical data, of Mr. Miless Brink, in the technical performance of the tests, and of Mr. Lawrence C. Johnson, in the statistical evaluation of the data.

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ELECTROPHORESIS OF SERUM PROTEIN IN ASTHMA

Preliminary Report

Rubens G. Ferri, Ernesto Mendes, M.D., Therezinha J. B. Cardoso, and Tiyo Tutiya, São Paulo, Brazil

After the description by Tiselius, in 1937, of protein separation by electrophoresis, numerous papers were published showing that there are changes in the distribution of the serum proteins in several diseases.

The most common change is the increase of gamma globulin, with a decrease in albumin, as is the case in portal and biliary cirrhosis, lupus erythematosis, myeloid leukemia, etc.[1]

In another group of diseases, the most evident changes occur in the alpha globulin fraction, as is the case in rheumatoid arthritis.[2]

However, depending upon the stage and type of disease, some qualitative changes can be observed, as reported by MacKay,[1] in portal cirrhosis. In this case, two gamma globulins are present.

The beta globulin, which in normal serum appears as one band when electrophoresis is carried out under normal conditions (Veronal-acetate buffer, pH 8.6; ionic strength 0.1), can be seen as a two-band pattern in sera from hepatosplenic schistosomosis.[3] A similar component, called *H*, was described by Violler and associates[4] in cases of liver diseases.

Cooke and his associates[5] reported an abnormal distribution of the protein fractions in the sera from asthmatic patients, using free electrophoresis. They found increased alpha globulins and occasionally an additional peak in alpha or beta regions.

Benda and Urquia[6] suggested that differences between sera of asthmatic and nonasthmatic patients must be qualitative and not quantitative.

In the present paper this question, as well as the relationship between the different forms of asthma, is investigated.

MATERIALS AND METHODS

Forty-four serum samples from forty-one asthmatic patients, with or without other allergic conditions, were studied. It was very difficult to classify the various types or forms of asthma, as the criteria commonly used are subjected to all kinds of criticisms. The patients were divided into three main groups—allergic, infectious, and "mixed group"—according to the length of illness, allergic history, reactions to infections, physical and psychologic agents, hemogram and sedimentation test, and allergic tests including skin tests and exclusion of allergens.

From the Department of Microbiology and Immunology, Faculty of Medicine, University of São Paulo, and Section of Allergy, Hospital das Clínicas, São Paulo, Brazil.

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A control group of thirty-eight persons was used; each person was questioned about general health, but a clinical examination was not made.

As a rule, all the sera were kept at –25° C. until analyzed and were thawed more than once only when an analysis was repeated. Total protein was studied by the method of Gornall and associates.[7] Filter paper electrophoresis was made according to the technique of Grassman and Hannig,[8, 9] using the "Elphor-H" apparatus. The volume of serum for the electrophoresis was 0.007 ml. Veronal-acetate buffer, pH 8.6, ionic strength 0.1, was employed. Migration time varied from twelve to sixteen hours, and the drying of the paper strips was done at room temperature. A saturated solution of amido-black (Amidoschwarz-10B-Bayer) in methyl alcohol containing 10 per cent (v/v) of acetic acid was used to stain paper strips. The washing solution

TABLE I. INDIVIDUAL VALUES OF PROTEIN FRACTIONS OF SERA FROM THE CONTROL GROUP

	RELATIVE CONCENTRATIONS					G./100 ML. OF SERUM					
NO.	ALBUMIN	ALPHA$_1$	ALPHA$_2$	BETA	GAMMA	TOTAL PROTEIN	ALBUMIN	ALPHA$_1$	ALPHA$_2$	BETA	GAMMA
17A	51.3	4.2	7.9	12.4	23.9	7.87	4.04	0.33	0.62	0.97	1.88
18A	55.1	4.0	7.7	14.3	21.5	7.44	4.09	0.29	0.57	1.06	1.60
20	56.7	6.1	11.8	10.5	14.8	7.00	3.97	0.42	0.83	0.74	1.04
21	51.6	7.0	6.9	13.2	21.0	—	—	—	—	—	—
22	50.0	5.2	9.2	10.9	24.7	—	—	—	—	—	—
23	51.7	5.9	11.2	14.0	17.0	—	—	—	—	—	—
25A	58.2	4.6	8.9	8.9	19.2	7.21	4.20	0.33	0.64	0.64	1.38
26A	52.8	5.8	12.0	12.8	16.5	8.31	4.37	0.42	1.00	1.06	1.47
27A	48.2	2.5	11.6	15.3	22.1	7.00	3.37	0.17	0.81	1.07	1.55
28A	58.3	6.5	9.7	9.4	15.9	7.40	4.31	0.48	0.72	0.69	1.18
29A	61.4	5.2	5.8	9.9	17.6	7.79	4.78	0.41	0.45	0.77	1.37
38	60.3	4.8	8.6	9.0	17.2	7.21	4.34	0.34	0.62	0.65	1.24
39	55.9	8.6	11.2	9.0	15.1	7.43	4.15	0.64	0.83	0.66	1.12
40	47.2	6.5	12.6	10.9	22.7	8.30	3.91	0.54	1.04	0.90	1.88
146	47.1	4.4	10.8	13.2	24.4	6.86	3.23	0.30	0.74	0.90	1.67
147	51.7	3.2	7.7	11.4	25.9	7.38	3.81	0.23	0.57	0.83	1.91
148	46.6	5.8	9.8	12.1	25.6	7.12	3.31	0.41	0.69	0.86	1.82
149	47.9	8.3	10.6	11.0	23.3	—	—	—	—	—	—
151	48.5	5.1	8.8	11.6	25.9	7.64	3.70	0.38	0.67	0.88	1.97
152	62.0	4.7	7.5	9.9	15.7	6.25	3.87	0.29	0.46	0.62	0.98
43	60.3	3.1	10.2	10.8	15.5	7.00	4.22	0.21	0.71	0.75	1.08
159	48.4	6.6	11.1	12.6	21.2	7.45	3.60	0.49	0.82	0.93	1.57
163	46.6	11.1	9.7	11.9	20.7	7.47	3.48	0.82	0.72	0.88	1.54
200	57.4	4.4	9.3	10.4	18.4	6.63	3.80	0.29	0.61	0.68	1.21
201	58.3	4.7	6.5	9.6	20.8	6.92	4.03	0.32	0.45	0.66	1.43
202	56.9	8.2	8.2	11.3	15.3	6.78	3.85	0.55	0.55	0.76	1.04
203	51.4	5.8	6.0	9.8	26.9	7.32	3.76	0.42	0.44	0.71	1.96
204	48.7	6.5	9.8	10.9	23.8	6.82	3.32	0.44	0.67	0.74	1.62
208	55.1	5.2	8.7	9.7	21.2	—	—	—	—	—	—
209	51.9	4.6	8.5	8.9	26.1	7.53	3.90	0.34	0.63	0.67	1.96
210	51.8	5.7	6.7	13.2	22.5	6.63	3.43	0.38	0.44	0.87	1.49
32	59.3	4.2	10.5	9.2	16.5	7.21	4.27	0.30	0.76	0.66	1.19
33	57.4	2.7	6.7	10.2	22.9	7.66	4.39	0.21	0.51	0.78	1.75
34	43.1	8.0	11.5	11.9	25.2	7.44	3.21	0.59	0.85	0.88	1.87
56	51.0	12.0	11.8	11.1	13.9	7.00	3.57	0.84	0.83	0.78	0.97

employed to remove the excess of amido-black was an aqueous solution of phenol (4 per cent W/v) with 10 per cent of acetic acid; and to remove the phenol, a 10 per cent solution of acetic acid (v/v) in methyl alcohol was used. After drying, the paper strips were made translucent by "Transparenzöl-Elphor" (adpha-brom-naphthalene in mineral oil) and then densitometric

readings were taken. The curves were studied by the geometric method of Hoxter and Mungioli,[10] in which each component is transformed into a gaussian curve. Components that did not produce neat peaks were deduced from the differences between the total height given by densitometric readings at each point and the height of the adjacent gaussian curves constructed by the same geometric method. Those points form a new gaussian curve whose area may be calculated.

RESULTS

Three of thirty-eight control sera showed a component migrating between beta and gamma globulins, with relative concentrations of 1.6, 4.1, and 4.5 per cent. The protein fractions calculated for the control group are presented in Table I.

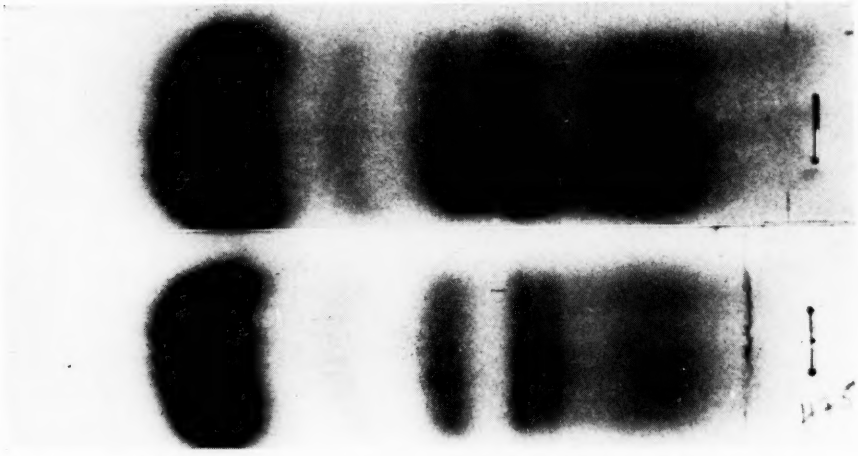

Fig. 1.—Photograph of paper strips. *A*, Normal serum; *B*, serum of asthmatic patient showing X component between beta and gamma.

According to the electrophoretic behavior, two main groups in sera of asthmatic patients were observed: (a) sera with the components of a normal serum and (b) sera presenting an extra component migrating between beta and gamma globulins.

Twenty-two asthma sera of the forty-four analyzed showed this extra component, which will be called X component (Table II). In nine sera the X component was perfectly separated from the beta globulin and clearly visible on the paper strip (Fig. 1, *B*). Fig 2, *A* and *B* shows graphs obtained from the paper strips corresponding to the sera presented in Fig. 1.

In the remaining thirteen sera, the X component did not reach a high level; thus, it was impossible to detect it in the paper strips. The curve obtained by densitometric readings between beta and gamma globulins was higher in such cases than in the control group (Fig. 2, *A* and *C*). In these figures *Ap.* indicates the application point. In constructing the gaussian curves for beta and gamma globulins, an apparently free area between these com-

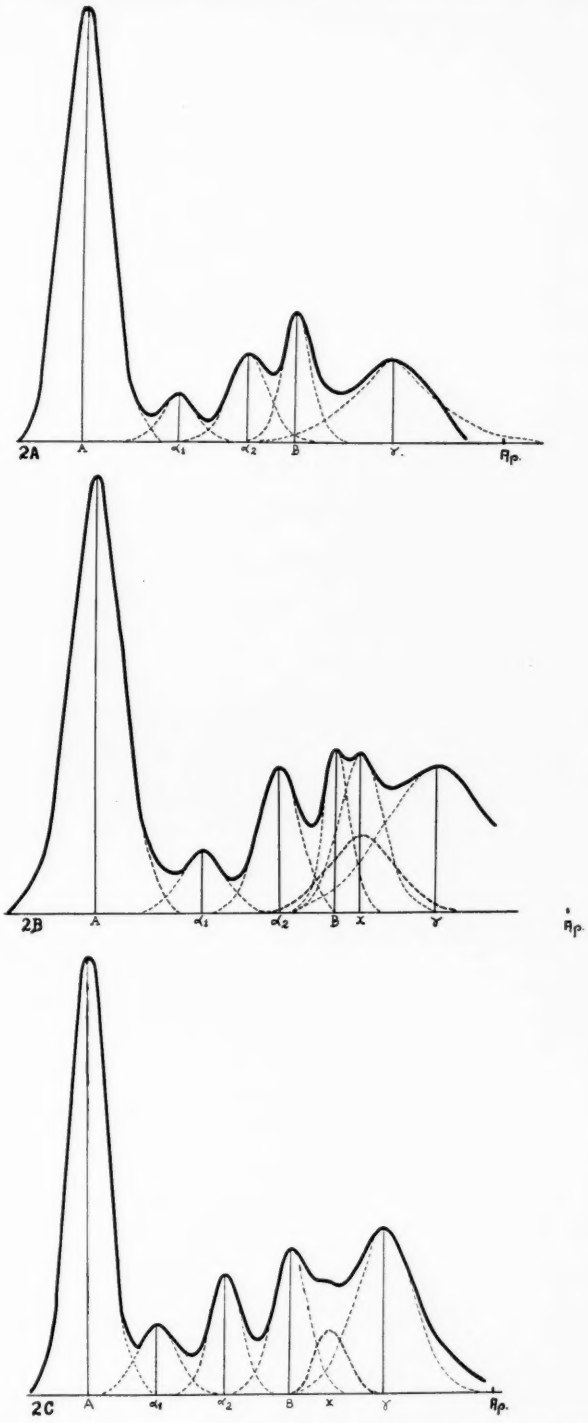

Fig. 2.—Densitometric curves. *A*, Normal serum shown in Fig. 1, *A*; *B*, asthma serum shown in Fig. 1, *B*; *C*, asthma serum containing X component which was not seen as a separate band.

TABLE II. INDIVIDUAL VALUES OF PROTEIN FRACTIONS OF SERA FROM ASTHMATIC GROUP

	RELATIVE CONCENTRATIONS						G./100 ML. OF SERUM							
NO.	ALBUMIN	$ALPHA_1$	$ALPHA_2$	BETA	X	GAMMA	TOTAL PROTEIN	ALBUMIN	$ALPHA_1$	$ALPHA_2$	BETA	X	GAMMA	TYPE OF ASTHMA†
31*	49.0	5.8	11.7	13.4	7.4	12.5	5.68	2.78	0.33	0.66	0.76	0.42	0.71	A
137*	52.1	2.7	11.0	7.8	6.4	19.9	6.92	3.60	0.18	0.76	0.53	0.44	1.37	M
158*	48.7	6.4	12.8	10.5	2.7	18.9	6.63	3.23	0.42	0.84	0.69	0.18	1.25	M
168	41.8	10.3	15.2	10.8	1.9	19.9	6.98	2.91	0.72	1.06	0.75	0.13	1.38	M
171	44.4	6.9	10.6	12.3	7.5	18.0	7.32	3.25	0.50	0.77	0.90	0.55	1.32	M
175	50.7	4.1	12.6	9.2	4.6	19.0	7.64	3.87	0.31	0.94	0.70	0.35	1.45	M
48	55.9	2.7	9.1	16.7	2.0	13.5	8.31	4.64	0.22	0.76	1.38	0.16	1.12	I
156*	41.4	4.5	7.4	8.5	3.5	34.6	7.12	2.94	0.32	0.52	0.60	0.24	2.46	M
30A*	41.0	1.8	5.6	9.9	5.0	36.5	7.87	3.22	0.14	0.44	0.78	0.39	2.87	M
67	41.3	6.9	9.5	12.9	5.0	24.3	7.87	3.25	0.54	0.75	1.01	0.39	1.91	I
71	45.1	6.5	7.6	11.6	4.1	25.0	6.56	2.95	0.43	0.49	0.76	0.27	1.64	I
132*	41.2	5.0	10.6	4.9	10.0	28.2	6.78	2.79	0.33	0.71	0.33	0.67	1.91	M
140*	32.8	10.1	11.7	8.3	3.1	34.0	7.83	2.56	0.79	0.91	0.65	0.24	2.66	I
166	41.1	7.6	10.2	9.3	2.3	29.5	7.81	3.20	0.59	0.79	0.72	0.18	2.30	A
169	39.5	8.9	13.2	11.6	2.7	24.1	6.82	2.69	0.60	0.90	0.79	0.18	1.64	I
173*	42.5	10.5	10.5	4.5	7.2	24.8	6.92	2.94	0.72	0.72	0.31	0.49	1.72	A
178	44.9	8.2	11.5	11.0	2.7	21.7	6.86	3.07	0.55	0.78	0.75	0.18	1.48	M
185	39.1	10.3	9.6	12.4	3.3	25.2	6.35	2.48	0.65	0.60	0.78	0.20	1.60	M
86	51.7	5.0	12.4	9.9	2.0	20.9	6.65	3.43	0.33	0.82	0.65	0.13	1.39	A
127	45.0	5.0	10.3	13.3	1.9	24.4	7.32	3.29	0.36	0.75	0.97	0.13	1.78	M
193	34.2	9.1	13.3	9.3	2.7	31.4	6.98	2.38	0.63	0.92	0.65	0.18	2.19	
172*	34.6	8.3	7.8	7.1	5.8	28.4	7.26	2.51	0.60	0.57	0.51	0.42	2.05	A
15	45.9	6.7	6.8	8.8	3.0	28.7	6.73	3.08	0.45	0.45	0.59	0.20	1.93	A

7	44.9	6.7	10.9	13.9	23.1	7.87	3.42	0.53	0.86	1.09	1.82	M
81	46.1	5.4	10.6	16.0	21.8	7.87	3.62	0.42	0.83	1.25	1.71	M
92	43.9	5.7	12.9	11.5	26.0	7.65	3.35	0.43	0.98	0.88	1.98	A
99	43.9	5.4	10.4	17.5	22.7	6.96	3.05	0.37	0.72	1.22	1.58	A
110	49.4	4.4	10.2	8.7	27.2	7.80	3.85	0.34	0.79	0.67	2.12	M
160	35.1	8.2	12.6	14.5	29.6	7.68	2.69	0.63	0.96	1.11	2.27	M
161	38.2	8.4	12.4	11.3	29.7	6.86	2.62	0.57	0.85	0.77	2.03	A
164	42.9	5.0	11.7	13.9	26.3	6.72	2.88	0.33	0.78	0.93	1.76	A
165	40.3	8.0	15.1	9.5	27.0	6.63	2.66	0.53	1.00	0.63	1.79	A
167	42.6	6.4	9.5	8.8	32.8	7.42	3.16	0.47	0.70	0.65	2.43	A
170	44.9	10.1	11.0	10.1	23.8	7.32	3.28	0.73	0.80	0.73	1.74	A
184	36.1	6.7	14.6	12.5	30.0	7.64	2.76	0.51	1.11	0.95	2.29	A
197	40.8	6.9	12.6	12.4	27.3	7.42	3.02	0.51	0.93	0.91	2.02	
8	46.8	10.4	9.5	10.7	25.5	—	—	—	—	—	—	I
13	62.5	5.5	5.1	4.9	21.7	7.40	4.62	0.40	0.38	0.36	1.61	A
9	53.2	4.4	9.4	9.6	23.4	7.87	4.18	0.35	0.74	0.75	1.84	A
14	54.0	7.7	9.5	9.2	19.6	7.81	4.21	0.60	0.74	0.71	1.53	M
85	55.4	4.5	13.2	10.0	17.0	7.65	4.23	0.34	0.99	0.76	1.29	A
87	55.0	5.1	13.6	9.5	16.8	7.30	4.00	0.37	0.98	0.69	1.22	A
114	58.5	4.8	10.5	10.1	15.9	7.18	4.20	0.34	0.76	0.72	1.14	I
162	40.2	8.3	10.6	12.5	28.3	7.12	2.86	0.59	0.75	0.89	2.02	M

The X component could be seen directly in the paper strips.
†A = Allergic.
M = Mixed.
I = Infectious.
Note: Samples 172 and 99 are from the same patient, taken with several months' interval. The same is true for samples 7 and 13, 9 and 15.

TABLE III. AVERAGE VALUES OF PROTEIN FRACTIONS OF SERA FROM CONTROL AND ASTHMATIC GROUPS

	ALBUMIN	ALPHA$_1$	ALPHA$_2$	BETA	GAMMA	X COMPONENT
			Relative Concentrations			
Control (35 cases)	53.14 ± 4.92*	5.74 ± 2.06	9.30 ± 1.86	11.17 ± 1.64	20.57 ± 3.89	
Asthma (44 cases)	44.97 ± 6.69	6.62 ±2.18	10.84 ± 2.26	10.70 ± 2.80	24.52 ± 5.47	4.27 ±2.20†
Values of t found	5.96 P $<$0.001	1.83 P $>$0.05	3.20 P $>$0.0001 $<$0.01	0.87 P $>$0.4	3.59 P $<$0.001	
			Absolute values in G./100 ml.			
Control (30 cases)	3.87 ± 0.39	0.406 ± 0.15	0.67 ± 0.15	0.80 ± 0.13	1.49 ± 0.32	
Asthma (43 cases)	3.25 ± 0.58	0.466 ± 0.15	0.78 ± 0.16	0.77 ± 0.22	1.79 ± 0.46	0.299 ± 0.14
Values of t found	5.17 P $<$0.001	2.0 P $\leqslant$ 0.05	3.66 P $<$ 0.001	0.67 P $>$0.5	3.06 P $>$0.001 $<$0.01	

*Standard deviation.
†Average value for the 22 cases which presented the X component.

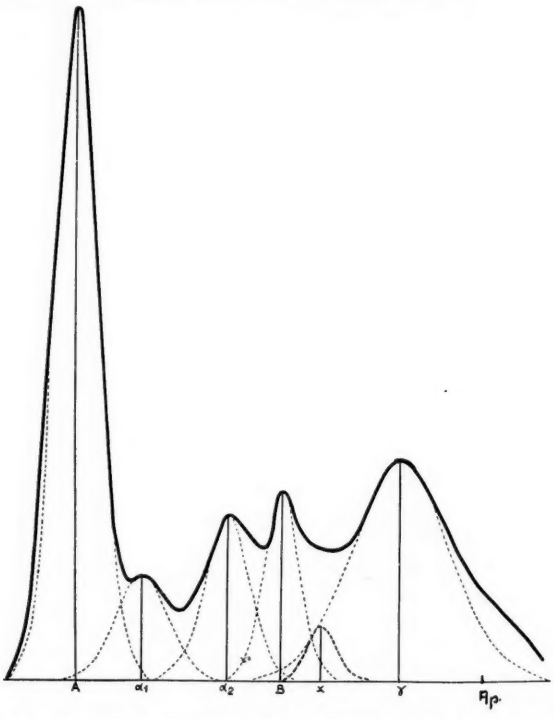

Fig. 3.—Densitometric curve of serum 166; X component representing 2.3 per cent of the total protein.

ponents will appear which would not exist if such an area were not occupied by proteins that are able to take up the dye. Figs. 3, 4, and 5 show the X component as 2.3, 3.5, and 7.4 per cent of the total protein. Table III gives the relative and absolute average values of all the fractions of both asthmatic and control groups.

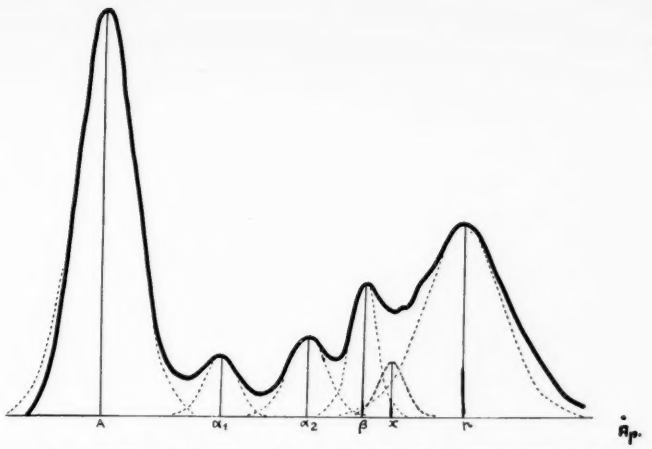

Fig. 4.—Densitometric curve of serum 156; X component representing 3.5 per cent of the total protein.

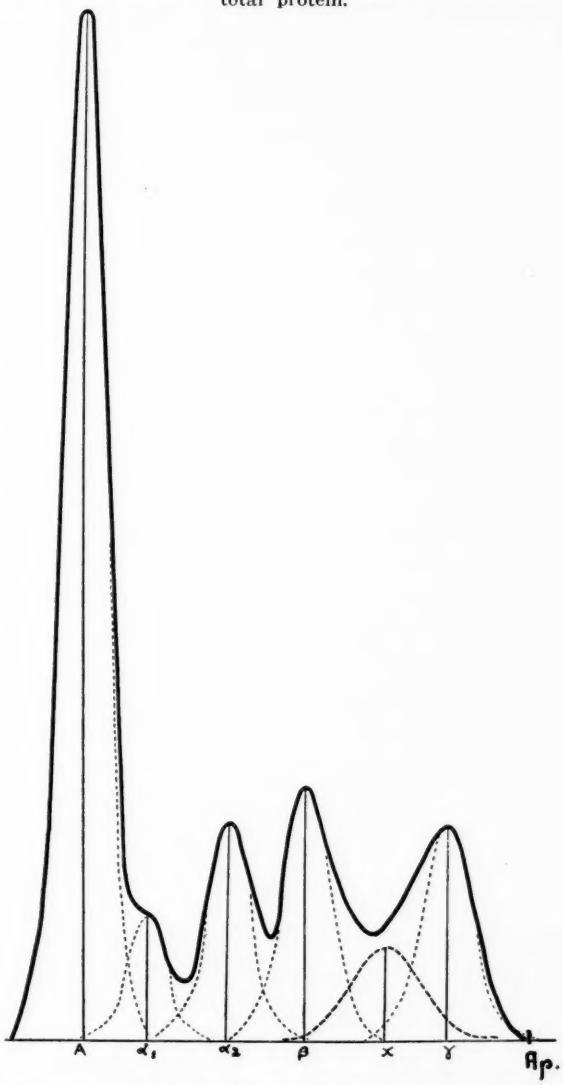

Fig. 5.—Densitometric curve of serum 31; X component representing 7.4 per cent of the total protein.

The analyses of these data by the "t" test revealed that in the asthmatic group the albumin is obviously decreased and the alpha$_2$ and gamma globulins increased. The alpha$_1$ globulin is just within the limit of normality and the beta globulin does not differ from the controls.

DISCUSSION

Since the electrophoretic analyses of sera of nonasthmatic patients revealed a great diversity, it will be necessary to study a greater number of normal persons, under rigorous clinical control, to obtain representative values for the healthy population. The three cases in the control group which presented X component were not computed because they could be considered abnormal. In Chile, Madrid* found an extra component in the beta globulin region in 27 per cent of supposedly normal people. The methods and materials used by Madrid are, however, different from ours. If we trace individual curves with the values of different serum fractions for both the control and asthmatic groups, we will find that they overlap and that some values that fall within both curves can be attributed to material either from the normal group or from the group of patients with asthma.

The asthma cases were classified as follows: seventeen allergic, seven infectious, and seventeen "mixed" type. In the allergic type four had X component (23.5 per cent), in the mixed type nine had X component (52.9 per cent), and in the infectious type five presented it (71.4 per cent). However, the statistical analysis made in accordance with Fisher's[11] indications showed no significance of the last distribution. In order to judge it, a greater number of cases must be studied.

SUMMARY

We studied forty-four samples of sera from asthmatic patients and thirty-eight from nonasthmatic persons, employing filter paper electrophoresis by the method of Grassmann and Hannig. An abnormal distribution of the protein in fractions was found. An extra component migrating between the beta and gamma globulins was also found in about 50 per cent of the asthma cases, which were divided into three groups—allergic, infectious, and mixed as based upon laboratory and clinical data.

The statistical analysis of the average values for each protein fraction revealed decrease in albumin, increase in alpha$_2$ and gamma globulins, and no significant difference between the average values of beta and alpha$_1$ globulins.

ADDENDUM

After this paper was prepared, we received a copy of the *Journal of Clinical Pathology,* in which there appears an article by Consden and Powell[12] with a study of the separation of beta$_2$ globulin from normal sera, using special techniques, and borate or borate-barbitone buffers.

*Personal communication (1955).

Attention must be paid to the conditions and freshness of the sera, in order to avoid confusion of this beta$_2$ globulin with our so-called "X component" which, in fact, could be also a beta$_2$ globulin. It is important to observe that, using the same techniques and conditions for both normal and pathologic samples, the appearance of the extra component was highly frequent in the latter, while it was very uncommon in the normal sera.

Grateful acknowledgments are due Dr. Michel Rabinowitch for assistance in the statistical calculations.

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ADRENAL FUNCTION IN ALLERGY

I. Plasma 17-Hydroxycorticosteroid Concentrations in Children With Bronchial Asthma

Sheldon C. Siegel, M.D., Robert S. Ely, M.D., Victor Birnberg, M.D., and Vincent C. Kelley, M.D., Ph.D., Los Angeles, Calif.

FOR many years the adrenal gland has been known to be related in some way to diseases of hypersensitivity. As early as 1922, Kepinow[1] demonstrated that guinea pigs with impaired adrenal function appeared to have exaggerated anaphylactic reactions. Later experiments[2-4] showed that adrenalectomized animals were more susceptible to anaphylactic shock as well as to the administration of histamine. However, it is only recently that interest has been focused sharply on the adrenal cortical hormones and their relationship to allergy. Although numerous animal experiments have been performed in an attempt to elucidate this relationship, relatively few studies have been reported concerning the state of adrenocortical activity in atopic human subjects, and the conclusions from these have been contradictory. Eriksson-Lihr and his associates,[5] on the basis of epinephrine and insulin response tests, concluded that the majority of their patients with asthma had abnormal adrenal function. On the other hand, Quarles van Ufford,[6] using the Thorn test as an index of adrenal function, studied 335 asthmatic patients and inferred that most of them had normal adrenal function and that therefore steroids could not be considered as specific replacement therapy. Both of these studies employed indirect tests of adrenal cortical function which no longer are considered to be valid. Israels and his co-workers[7] found that the urinary excretion of 17-ketosteroids was lower than normal in young asthmatic patients, even though it varied with age and with evidence of infection. Several other investigators, measuring urinary-reducing corticoids as well as 17-ketosteroids, have found the urinary excretion of these hormones to be less in asthmatic patients than in normal persons.[8-14]

In recent years, new techniques have been developed which permit a more direct evaluation of adrenal cortical function. One of these is the method developed by Nelson and Samuels[15] which measures the concentration of plasma 17-hydoxycorticosteroids. Included in this group of steroids are cortisone and hydrocortisone, the latter being the principal adrenocortical hormone.[16-18]

From the Children's Medical Group, Los Angeles; Department of Pediatrics, School of Medicine, University of California, Los Angeles; Harbor General Hospital, Los Angeles; and the Department of Pediatrics, University of Utah College of Medicine, Salt Lake City, Utah.

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The present investigation was undertaken as part of an extensive study employing modern techniques in an attempt to further elucidate the status of adrenocortical activity in allergic children. In this initial report, data concerning plasma 17-hydroxycorticosteroid (17-OHCS) levels in children with various stages of severity of bronchial asthma are presented. Also, data concerning the influence of therapy with prednisone* or prednisolone* on these plasma 17-OHCS concentrations are included.

METHODS

The subjects of this study were fifty-seven children with bronchial asthma, ranging in age from 5 months to 13 years, who were selected from the Harber General Hospital Pediatric Allergy Clinic and from the private practice of one of us (S. S.). The severity of the asthma was classified into the following categories: asymptomatic, mild, moderate, and severe. Asthmatic patients classified as mild manifested no visible outward signs of respiratory distress but had positive findings of wheezing on auscultation of the lungs. Those classified as moderate had definite physical findings of respiratory distress with visible and auditory signs of dyspnea and wheezing. Patients diagnosed as having status asthmaticus were classified as severe. Each patient was assigned his clinical classification at the time his blood sample was obtained; however, this classification was not known by the laboratory staff who performed the plasma 17-OHCS determinations.

In some of the children, plasma samples were obtained in more than one stage of severity of their disease. In addition, serial specimens were obtained from some of the children during therapy with varying doses of prednisone and prednisolone. Control specimens were obtained from thirty-two normal, apparently healthy children residing in Los Angeles. After the blood was withdrawn, it was immediately placed in heparinized tubes and centrifuged; the plasma was kept frozen† until used for the determinations of the 17-hydroxycorticosteroid concentrations by the method of Nelson and Samuels.[15, 19]

RESULTS

The results of 118 determinations of plasma 17-OHCS in fifty-seven asthmatic children and of thirty-four determinations in thirty-two control children are shown in Table I. In the asthmatic children, thirty-seven determina-

TABLE I. RELATIONSHIP OF PLASMA 17-HYDROXYCORTICOSTEROID CONCENTRATIONS TO SEVERITY OF ASTHMA

	CONTROL	ASYMPTOMATIC	MILD	MODERATE	SEVERE
Number of samples	34	37	40	35	6
Number of patients	32	34	28	28	6
Mean 17-OHCS (mcg. %)	4.5	3.3	3.6	13.0	18.8
Standard error of mean	±0.77	±0.61	±0.61	±2.01	±7.61

*The prednisone and prednisolone were furnished through the courtesy of the Schering Corporation, Bloomfield, New Jersey, and the Upjohn Company, Kalamazoo, Michigan.

†Shipped air express in dry ice to Salt Lake City where the determinations of plasma 17-OHCS were made.

tions were made in thirty-four asymptomatic patients, forty determinations in twenty-eight patients with mild asthma, thirty-five determinations in twenty-eight patients with moderately severe asthma, and six determinations in six patients with severe asthma.

Despite the fact that the values within each of the four arbitrarily selected categories of severity varied considerably, there was observed a definite relationship between the degree of severity of asthma and the plasma 17-OHCS concentration. In the group of patients classified as asymptomatic and in that classified as mild, the plasma 17-OHCS concentrations were essentially the same, the mean values being 3.3 mcg. per cent and 3.6 mcg. per cent, respectively. Furthermore, these mean values did not differ significantly from the mean value of 4.5 mcg. per cent for the group of control children. However, in the moderately ill and in the severely ill patients the mean plasma 17-OHCS concentrations (13.0 mcg. per cent and 18.8 mcg. per cent, respectively) were significantly elevated as compared with those in the asymptomatic or mildly ill patients. The data clearly indicate that the asthmatic patient with exacerbation of his symptomatology tends to develop a higher plasma 17-OHCS level. The highest level (50.2 mcg. per cent) observed in any child in the entire group was that of the only child who died in status asthmatics, a 3½-year-old boy.

TABLE II. RELATIONSHIP OF PLASMA 17-HYDROXYCORTICOSTEROID CONCENTRATIONS TO PREDNISONE DOSE (11 PATIENTS)

	TOTAL DAILY DOSE OF PREDNISONE		
	2½ TO 10 MG.	12½ TO 15 MG.	20 TO 30 MG.
Mean 17-OHCS (mcg. %)	4.7	11.1	30.6
Standard error of mean	±1.15	±2.20	±2.47
Number of samples	25	13	5
Number of patients	8	7	4

Plasma 17-OHCS concentrations also were determined in a group of patients receiving prednisone or prednisolone therapy. Table II shows the data concerning these concentrations in patients receiving prednisone in various doses. In these patients the plasma samples were obtained at random without regard to the time elapsed after administration of the drug. In those

TABLE III. RELATIONSHIP OF PLASMA 17-HYDROXYCORTICOSTEROID CONCENTRATIONS TO PREDNISOLONE DOSE (10 PATIENTS)

	TOTAL DAILY DOSE OF PREDNISOLONE	
	2½ TO 10 MG.	12½ TO 15 MG.
Mean 17-OHCS (mcg. %)	8.2	15.0
Standard error of mean	±1.89	±2.93
Number of samples	8	6
Number of patients	7	6

patients receiving 2.5 to 10 mg. prednisone per day, the mean plasma 17-OHCS concentration was 4.7 mcg. per cent, a value which does not differ significantly from the mean value in asymptomatic or mild asthmatic patients not receiving hormone therapy. However, in those patients receiving 12.5 to 15 mg. per day and in those receiving 20 to 30 mg. per day, the mean plasma 17-OHCS con-

centrations—11.1 mcg. per cent and 30.6 mcg. per cent, respectively—differed significantly from each other and both were significantly higher than the concentrations in patients with asymptomatic or mild asthma or those in patients receiving 2.5 to 10 mg. prednisone per day.

The data of Table III show that a similar relationship exists between the dose of prednisolone and the resultant plasma 17-OHCS concentrations. In those patients receiving 2.5 to 10 mg. per day, the mean plasma 17-OHCS concentration was 8.2 mcg. per cent; in those receiving 12.5 to 15 mg. per day it was 15.0 mcg. per cent. These two values differ significantly from each other, and the data suggest that that plasma 17-OHCS concentration is proportional to the dose of prednisolone administered.

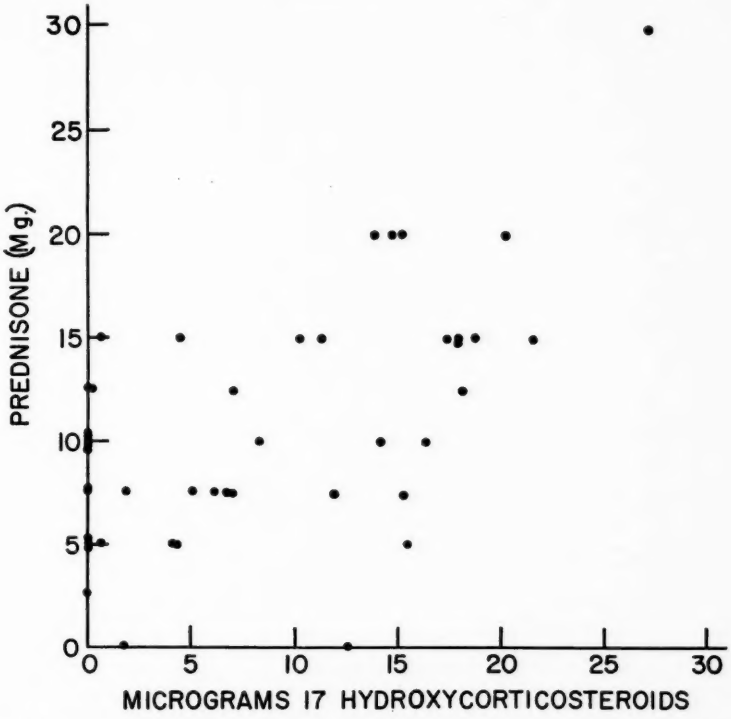

Fig. 1.—Relationship of prednisone dose to level of plasma 17-hydroxycorticosteroids.

Figs. 1 and 2 illustrate graphically the correlation between dose of drug and plasma 17-OHCS concentration. Fig. 1 shows a scattergram illustrating this relationship for patients receiving prednisone. From this graph, it is apparent that there is a linear correlation between the dose of prednisone and the plasma 17-OHCS concentration. Statistically, the coefficient of linear correlation (r) is 0.64, which indicates a highly significant correlation. Fig. 2 shows in a similar manner the data relating dose of prednisolone to plasma 17-OHCS concentration. In the case of this drug, also, there is a highly significant correlation, r being 0.67.

DISCUSSION

Only during the last several years have methods become available for directly determining the concentrations of adrenocortical hormones in body fluids.[20] The development of these methods has been made possible by improvements in the procedures for hormone extraction and separation and by the introduction of reagents for more specific color development. As a result of the development of these methods, more definitive information concerning the secretion

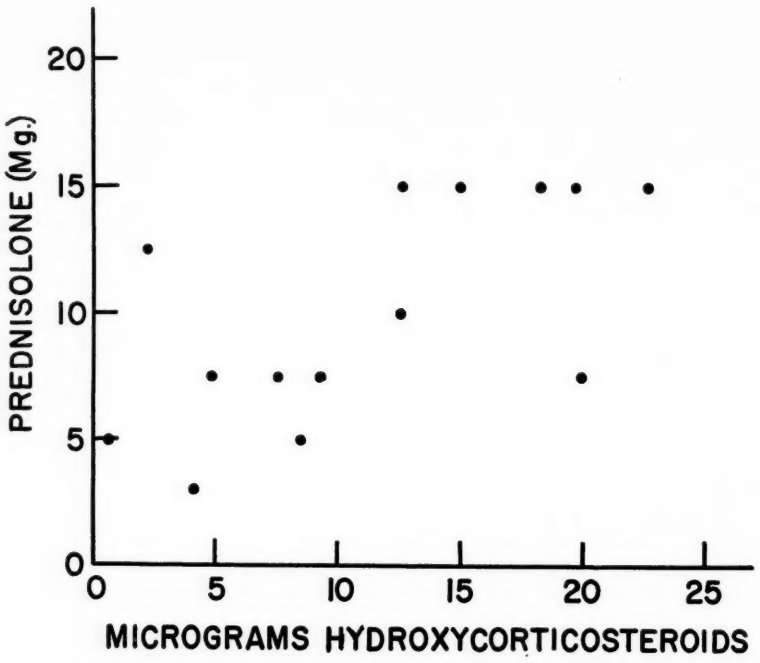

Fig. 2.—Relationship of prednisolone dose to level of plasma 17-hydroxycorticosteroids.

of adrenocortical hormones and their subsequent metabolism now may be obtained. Such information includes data concerning the circulating concentrations of these hormones under ordinary conditions and following administration of stimulating agents, such as ACTH; the rate of disappearance of exogenously administered hormone; comparison of the ratio of free, or active, hormone to the conjugated, or inactive, form; and the urinary excretion of these hormones under various conditions.

This initial report concerning studies of adrenocortical function in allergic children is confined to a consideration of data regarding circulating concentrations of hormones of the 17-hydroxycorticosteroid (17, 21-dihydroxy-20-keto) type in asthmatic children, with and without hormone therapy. More extensive evaluation of adrenocortical function and steroid metabolism in allergic children is in progress and will be reported in future communications. The Nelson and Samuels technique[15, 19] employed in this study, and all other techniques which measure 17-hydroxycorticosteroids are based upon the Porter-Silber[21] reaction,

which involves color development with sulfuric acid-phenylhydrazine and is specific for those hormones having a 17, 21-dihydroxy-20-ketosteroid configuration. These include compounds S, E, and F and certain of their derivatives. As shown in Fig. 3, the synthetic steroids, prednisone and prednisolone, differ from the parent compounds, cortisone and cortisol (hydrocortisone), only by having an additional double bond in ring A. Since they contain the essential 17, 21-dihydroxy-20-keto configuration, theoretically they should be measured by the method used. It recently has been demonstrated[22] that they are measured quantitatively by the Nelson and Samuels method.

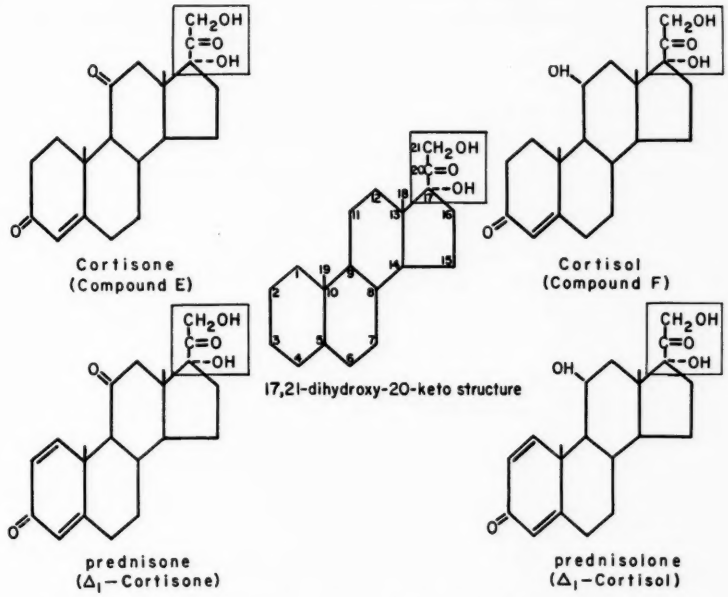

Fig. 3.—Structural characteristics of prednisone and prednisolone.

It can be seen from Table I that the mean plasma 17-OHCS values of 3.3 and 3.6 meg. per cent for the asthmatic patients classified as a symptomatic and as mild, respectively, do not differ significantly from the mean value of 4.5 meg. per cent for the group of control children. The finding of this low plasma 17-OHCS concentration in the control children deserves comment. A variety of different "normal values" for plasma 17-OHCS concentrations have been reported by various investigators working at different geographical sites.[23, 24] There appears to be no age or sex difference contributing to these mean steroid values. The somewhat divergent results obtained by different investigators have been presumed due to variations in the techniques used. In this study, however, plasma samples from the group of normal children residing in Los Angeles were shipped to Salt Lake City where the 17-OHCS concentrations were determined simultaneously with samples from that area. The mean plasma 17-OHCS value obtained in that laboratory for normal children residing in the Salt Lake City area is 12.0 ± 1.29 meg. per cent.[28] The

difference between this and the mean value of 4.5 ± 0.77 mcg. per cent obtained by the same laboratory for children residing in the Los Angeles area is highly significant.

The reasons for this difference of normal mean values are not completely apparent. One partial explanation for the difference is the variation in the time the samples were drawn. It has been well established that a diurnal variation of the 17-OHCS levels, high in the morning and with a progressive decrease through the day, occurs in normal persons.[24, 26] Since specimens from the asthmatic patients of necessity had to be taken at varying times throughout the day, the control specimens of the Los Angeles children were taken in a similar manner. On the other hand, the Salt Lake City control specimens were obtained in the morning, and this difference in time of collecting specimens undoubtedly partially accounts for some of the discrepancy between the normal values. Other factors which potentially might influence the values obtained, such as technique of sample collection, delay in separating plasma, and the methods of storing samples, were investigated carefully; these did not differ in the Los Angeles and Salt Lake City areas. Therefore, it is conceivable that some environmental or other factor (rather than variation in technique) accounts for the low values found in the Los Angeles group of normal children. Clearly, more extensive investigation of this matter is necessary. A similar comparison of the values in normal adults from the two areas is in progress.

In the groups of patients with moderately severe and with severe asthma, the mean plasma 17-OHCS values were consistently higher than those in the asymptomatic group or the group with mild asthma. One might well interpret this as evidence of adrenocortical response to the "stress" of their disease; this interpretation is in agreement with Israels' observation[7] of increased urinary 17-ketosteroid excretion during activation of the disease or respiratory infection. However, an important question is whether this response is as great as that which would occur in a normal child presented with a "stress" situation of the same magnitude. Unfortunately, this question cannot be answered on the basis of present data. The circulating 17-OHCS concentration alone provides insufficient evidence, since this concentration at any given moment may be high as a result of increased production, decreased destruction or "utilization," or a combination of factors, and does not necessarily reflect accurately the rate of secretion by the adrenal cortex. From these data regarding plasma 17-OHCS and Israels' data[7] regarding urinary steroid excretion, it appears that moderately severe and severe asthmatics do respond to the "stress" of their disease by an elevation of plasma 17-OHCS. It is apparent, though, that this elevation is not adequate to protect them against their disease, since the symptomatology continues. The fact that the administration of additional steroids has a beneficial influence upon the severity of the symptomatology is interpreted by us as meaning that although the asthmatic patient does exhibit an adrenal response to "stress," this response is inadequate to meet the demand.

Although the asthmatic groups classified as asymptomatic or mild had low mean circulating 17-OHCS concentrations, these values were not significantly

lower than that of the control group. From this, it is obvious that a person need not have asthma because he has a low plasma 17-OHCS concentration. On the other hand, the consistently low plasma 17-OHCS concentrations observed in the asymptomatic and mild asthmatic groups may indicate that one of the factors which makes a person susceptible to asthma is a low basal rate of secretion of 17-hydroxycorticosteroids. This interpretation would be in accord with data presented by several previous authors[7-14] who have reported decreased urinary excretion of 17-ketosteroids and reducing corticoids by allergic patients. The data presented in this report do not justify any final conclusion in this regard because, although the plasma 17-OHCS concentrations are consistently low in the asymptomatic and mild asthmatic groups, the mean values for these groups are not significantly lower than that for the Los Angeles control group. The exceptionally low value found in the control group in this study has been discussed; therefore, this study is being expanded to include patients with bronchial asthma from the Salt Lake City area, where a higher normal mean plasma 17-OHCS concentration prevails.[24, 27, 28]

A highly significant correlation was found between the amount of prednisone or prednisolone administered and the resultant plasma 17-OHCS concentration (Tables II and III, Figs. 1 and 2). However, among the groups of hormone-treated patients, only in that group receiving 20 to 30 mg. prednisone per day was the mean plasma 17-OHCS concentration higher than those observed in the untreated moderately severe and severe asthmatic children. Several factors probably account for this finding. Since the production of ACTH is suppressed by administration of prednisone or prednisolone, the endogenous secretion of 17-OHCS in turn also is suppressed and the plasma 17-OHCS values measured represent the exogenous hormones. Furthermore, since plasma samples were obtained at variable intervals after the exogenous steroid was administered, the plasma 17-OHCS values measured do not represent the peak concentrations attained. It is known that plasma 17-OHCS concentrations become elevated but return to or below base line values four to six hours after exogenous hormone is administered[22]; hence, randomly obtained plasma samples from patients receiving hormone therapy show quite great variability and may be very low. In a previous report,[35] it was shown that in patients receiving as much as 50 mg. of cortisone per day or 40 I.U. of ACTH per day the mean plasma 17-OHCS concentrations observed by similar random sampling were not significantly greater than control values.

It is well known from clinical experience that most allergic patients can be kept asymptomatic at a certain critical dose of the steroid hormones.[36] Small reductions below this maintenance dose often result in an exacerbation of symptoms. In view of this, and in view of the correlation found in this study between the dose of administered hormone and the plasma 17-OHCS levels, it was thought that in a patient on hormone therapy perhaps a critical plasma concentration of 17-OHCS could be demonstrated, below which he would show symptoms and above which he would be asymptomatic. In this study, no such critical level was demonstrated. Several reasons may account for this finding.

First, there are many factors other than drug dosage that influence the level of 17-hydroxycorticosteroids. Second, there are equally as many factors, other than hormone levels, which influence the severity of any allergy. Finally, in the patients studied, a very small reduction in prednisone or prednisolone dose (1 to 5 mg.) often was the margin of difference between asymptomatic and symptomatic states of the allergic manifestation. Such minute reductions in dose would not be reflected accurately by corresponding changes in the circulating 17-OHCS concentrations.

SUMMARY AND CONCLUSIONS

The results of 152 determinations of plasma 17-hydroxycorticosteroids in fifty-seven asthmatic and thirty-two normal children are reported. Plasma 17-hydroxycorticosteroid levels were determined in fifty-seven asthmatic children at four stages of their disease: asymptomatic, mild, moderate, and severe. In those patients with moderate or severe symptoms, the plasma levels of 17-OHCS were significantly higher than in the asymptomatic or mild groups or in the control group. In the patients whose asthma was asymptomatic or mild, the 17-hydroxycorticosteroid levels were not statistically different from those of normal controls.

The results of fifty-seven plasma 17-hydroxycorticosteroid levels determined in twenty-one allergic children receiving variable amounts of prednisone and prednisolone also are reported. The levels in these patients were found statistically to correlate directly with the amount of prednisone and prednisolone administered to the patient, but no critical hormone level at which the majority of the patients became asymptomatic could be determined.

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PREDNISONE (METICORTEN)* IN THE TREATMENT OF BRONCHIAL ASTHMA

A Clinical Study

Samuel J. Taub, M.D.,** Morris A. Kaplan, M.D.,*** and Abe L. Aaronson, M.D.,**** Chicago, Ill.

A CLINICAL study, comprising 153 patients suffering from severe bronchial asthma, was undertaken to determine whether or not prednisone would alleviate symptoms without the complicating side effects usually seen with cortisone, hydrocortisone, or ACTH.

Patients for this study were divided into three groups (Table I):

1. Patients hospitalized for status asthmaticus, initially treated with ACTH, intravenously, and maintained thereafter on prednisone.

2. Patients with acute asthma occurring with pollinosis or mold allergy, following upper respiratory infection, overexposure to an inhalant allergen, inadvertent ingestion of a food allergen, following administration of a drug or serum, and acute reaction following overdosage to a specific allergen.

3. Patients with chronic asthma complicated by chronic emphysema, bronchiectasis, pulmonary fibrosis, cor pulmonale, chronic pulmonary infection, chronic bronchitis, perennial allergic rhinitis, nasal polyposis, and cardiac asthma, who could not be controlled in the usual manner or who developed the "escape mechanism" from cortisone or hydrocortisone.

It has been noted by us, as well as by others, that patients placed on maintenance doses of corticosteroids for bronchial asthma may develop an exacerbation of symptoms despite such therapy, which we term the "escape mechanism." We feel that this phenomenon may occur due to the following sequence of events. Patients receiving corticosteroids develop a reduction in the production of endogenous adrenocortical secretions and become dependent on the exogenous source. This leads to a physiologically malfunctioning adrenal gland. When the adrenal gland is acutely stressed by overexposure to an allergen, intercurrent infection, accidental trauma, surgery, a general anesthesia, or an emotional upset, the gland is unable to produce the needed secretions. The pa-

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**Professor of Medicine, The Chicago Medical School; Professor of Medicine, Cook County Graduate School.
***Assistant Professor of Medicine, The Chicago Medical School.
****Assistant Professor of Medicine, The Chicago Medical School.

tient may now be suffering from adrenocortical suppression, insufficiency, exhaustion, or atrophy of the gland. Symptoms redevelop, and in some cases acute adrenal shock has been noted. The "escape mechanism" may be prevented by giving the patient who is receiving corticosteroids an increased amount of the drug or 20 to 40 units of a long-acting ACTH once or twice weekly and by giving an additional amount at any time a stress situation is anticipated or presents itself.

After the symptoms in all groups subsided, the usual allergic investigation and specific therapy was instituted.

Dosage and Management of Patients.—The usual regime consisted of an initial dose of 30 mg. divided into six equal doses of 5 mg. Following this period, which ranged from twenty-four to forty-eight hours, a therapeutic period of three to seven days' duration was started, with doses averaging from 20 to 30 mg. per day; following this period, patients were placed on maintenance therapy of 5 to 15 mg. per twenty-four hours, which lasted from weeks to months.

The average patient required from 100 to 120 mg. of prednisone in the first seven days. The dosage schedule was altered slightly to meet the needs of the individual patient, based on severity of symptoms, age, and response to the drug.

TABLE I. INDICATIONS FOR USE OF PREDNISONE IN BRONCHIAL ASTHMA

GROUP	INDICATIONS	ADULTS	CHILDREN	INFANTS	TOTAL
I	Post-status asthmaticus	22	1	0	23
II	Acute	50	29	2	81
III	Chronic	35	14	0	49
Totals		107	44	2	153

Slightly higher initial doses were used in adults as compared to children. A very small group of infants (under 2 years of age) were placed on smaller doses than any of the others. A slightly larger initial dose was given to patients who had been on ACTH, cortisone, and hydrocortisone and who showed little or no relief, and also in selected patients, namely, those with acute drug eruptions, reactions following overdosage in hyposensitizations, and those asthmatic patients with severe symptoms who were uncontrolled by other measures.

The patients who were hospitalized for status asthmaticus were usually treated with intravenous fluids with aminophylline, 5 per cent glucose, potassium chloride, ACTH, adrenalin, sympathomimetic amines, iodides, antibiotics, chloral hydrate, and oxygen, as indicated.

This regime is our usual routine in the control of status asthmaticus. As soon as the patient was relieved of the acute symptoms, prednisone therapy was instituted and was continued upon discharge.

While the patient was in the hospital the following laboratory procedures were employed: blood pressure, urinalysis, complete blood counts, sedimentation

rate, CRP studies, blood sugar and other chemistry studies, bacterial sensitivity studies on sputa, nose and throat cultures, weight charts, and electrocardiograms.

Our procedure was to give antibiotics to selected patients in whom an infectious component was suspected for a period of seventy-two hours or longer (Table II).

TABLE II. USE OF ANTIBIOTICS IN PATIENTS TREATED

GROUP	PATIENTS ON OR MAINTAINED BY ANTIBIOTICS	ADULTS	CHILDREN	INFANTS
I (Post-status asthmaticus)	Number of patients	22	1	0
	Number of antibiotics	16	1	0
	Maintenance antibiotics	3	0	0
II (Acute)	Number of patients	50	29	2
	Number of antibiotics	29	23	2
	Maintenance antibiotics	5	0	0
III (Chronic)	Number of patients	35	14	0
	Number of antibiotics	20	12	0
	Maintenance antibiotics	13	8	0

The patients with acute and chronic asthma were usually ambulatory and were observed at least once or twice weekly in our offices. Bacterial sensitivity studies, as previously mentioned, were continued in the follow-up of the patient.

TABLE III. RESULTS OF THERAPY

GROUP	RESULT	I.	T.	M.	I.	T.	M.	I.	T.	M.*
I (Post-status asthmaticus) 23	Emotional state improved	6	6	6	0	1	1	0	0	0
	Wheezing decreased	6	6	6	1	1	1	0	0	0
	Cough decreased	6	6	6	0	1	1	0	0	0
	Dyspnea decreased	6	6	6	0	1	1	0	0	0
	Expectoration decreased	6	6	6	0	1	1	0	0	0
	Appetite improved	6	6	6	1	1	1	0	0	0
	Need for other drugs decreased	2	4	6	0	0	1	0	0	0
	Weight gain	0	0	6	0	0	1	0	0	0
II (Acute) 81	Emotional state improved	14	14	14	16	23	29	2	2	2
	Wheezing decreased	0	9	12	0	14	29	0	2	2
	Cough decreased	0	10	12	0	16	29	0	1	2
	Dyspnea decreased	0	11	12	0	17	29	0	0	2
	Expectoration decreased	0	10	12	0	13	29	0	0	2
	Appetite improved	0	12	37	0	27	27	1	1	1
	Need for other drugs decreased	0	3	12	0	0	29	0	0	2
	Weight gain	0	0	14	0	0	15	0	2	2
III (Chronic) 49	Emotional state improved	8	20	26	13	13	13	0	0	0
	Wheezing decreased	0	10	14	0	8	10	0	0	0
	Cough decreased	0	18	22	0	8	10	0	0	0
	Dyspnea decreased	0	20	26	0	10	12	0	0	0
	Expectoration decreased	0	12	22	0	11	12	0	0	0
	Appetite improved	0	16	26	0	10	12	0	0	0
	Need for other drugs decreased	0	10	16	0	0	11	0	0	0
	Weight gain	0	0	20	0	0	10	0	0	0

*I. = Initial (24 to 48 hours).
T. = Therapeutic (3 to 7 days).
M. = Maintenance (8 days, weeks, or months).

The results in the children and infants were more readily noted than in the adults in relation to time and degree.

Results of Therapy.—The following symptoms were taken into consideration in evaluating the results of therapy: (1) emotional state, (2) ability to sleep, (3) increase in appetite, (4) feeling of well-being, (5) degree of wheezing, (6) severity of the cough and expectoration, (7) amount of dyspnea, and (8) weight gain.

In the hospitalized group, the first symptom noted in those receiving ACTH and/or prednisone was an improved emotional state in the first twenty-four hours. This state varied from a feeling of well-being and cheerfulnes to one of euphoria.

In the next twenty-four to forty-eight hours, the degree of wheezing, cough, dyspnea, and expectoration decreased; in some instances, the sputa became thin and clear, as compared to the thick, tenacious, and mucoid material that had been produced previously. In the next period the appetite improved and the ability to sleep and rest was noted. As the use of prednisone was continued, the need for additional drugs diminished so that in many instances the patient received only maintenance therapy of prednisone.

In the acute and chronic asthma patients, the same degree of improvement prevailed as in the hospitalized group, except that in the chronic group the need for additional drugs remained more or less constant due to long-standing complications and sequelae.

TABLE IV. SIDE EFFECTS (USUALLY NOTED IN PATIENTS ON MAINTENANCE THERAPY OF LONG DURATION)

SIDE EFFECT	POST-STATUS ASTHMATICUS	ACUTE	CHRONIC
Weight gain	7	31	32
Buffalo hump			1
Increased blood sugar		1	
Glycosuria		1	6
Amenorrhea		1	
Metrorrhagia			1
Hirsutism			
Acne			1
Demineralization			1
Epigastric distress		4	1
Hypertension		3	2
Moon facies			12
Retention of Na and fluids			3
Irritability		3	2
Diarrhea		2	2
Urticaria		1	1
Transient euphoria	1	1	
Insomnia		2	1
Mania		1	
Excessive perspiration			
Muscle cramps			3

Complications With Prednisone.—When this study was originally started, we felt that there was little evidence of side effects which had been previously noted with ACTH, cortisone, and hydrocortisone. However, as more patients were studied and followed for longer periods of time, the side effects that had been previously noted with ACTH, cortisone, and hydrocortisone developed to

a greater or lesser degree. These side effects can be expected when the dosage of prednisone is comparatively high, above 30 mg. a day, and is used over a prolonged period of time.

Because many of these patients had been given ACTH, hydrocortisone, or cortisone, and were already on a low-salt diet, we did not change this regime. While they were on prednisone alone, there were usually no diet restrictions.

DISCUSSION

The early reports on prednisone were so encouraging, the dose required was so much smaller than with the other corticosteroids, and the side reactions were so minimal that we undertook the study of this drug in a large series of bronchial asthma patients.

Levin[1] studied twenty-four children with prednisone and felt that it was approximately twice as effective as hydrocortisone on a weight basis.

Arbesman and Ehrenreich[2] studied seventeen patients with asthma and obtained good results in all but one. They found that the average dose of prednisone was usually about one-fifth that of cortisone, with little or no side effect.

Barach, Bickerman, and Beck[3] treated thirty patients with bronchial asthma for a relatively short period of time and noted that the side effects resembled those produced by the other corticosteroids, but were much milder.

Skaggs, Bernstein, and Cooke[4] studied eight asthma patients using prednisone and noted that none of the side reactions noticed with the other corticosteroids were seen in their patients after the use of the drugs for one month.

Schwartz[5] studied two patients with bronchial asthma for approximately three months and noted fewer side effects from prednisone as compared with the other steroids.

Sheldon, McLean, and Mathews[6] reported their studies of fifty-one patients with severe bronchial asthma. Their results indicate that the average initial dose was somewhere between 25 and 35 mg. per day, with a maintenance dose of 10 mg. daily. They noted improvement within one to two days, with control of symptoms in three to four days. These observers utilized respiratory function tests for maximum improvement at the end of five to seven days of therapy. Their side reactions include those usually seen with other corticosteroids, but the side reactions were much less severe.

Feinberg and Feinberg[7] reported on sixty asthmatic patients in which they obtained excellent results on an initial dose of 20 to 30 mg. per day and a maintenance dose of 10 to 15 mg. per day. These observers felt that the effective maintenance dose of prednisone as compared to cortisone was, roughly, 5 to 1. The side effects encountered were minimal as compared to those of cortisone; however, the patients were not treated for long periods of time.

Jenkins[8] reported his study on patients in which the initial dose was 30 to 40 mg. per day and the maintenance dose was 10 mg. daily. Marked improvement was noted in twelve to forty-eight hours. Minimal side reactions were reported. Many of the patients who had respiratory function studies showed marked increase in ventilatory capacity.

From our studies of 153 patients with various types of bronchial asthma, we can report that the usual dose required was 30 mg., divided into six doses during the first twenty-four to forty-eight hours.

The therapeutic period required an average of 15 to 20 mg. divided into three to four doses in a twenty-four hour period. The average maintenance dose was from 10 to 15 mg. divided into two to three doses in a twenty-four hour period.

Our observations indicated that prednisone is from four to five times more potent than cortisone, on a weight basis. In addition, the duration of effectiveness was from six to twelve hours, and in some patients it was as long as twenty-four hours.

In attempting to evaluate the results, we felt that a good way of expressing this data was to determine the number of patients who had complete relief of symptoms, partial relief of symptoms or no relief of symptoms from the standpoint of remissions.

All of these patients, as we previously indicated, had complete allergic investigations and were treated with specific hyposensitization and symptomatic therapy. It will be noted from Table V that in Group I, which consisted of twenty-three patients (twenty-two adults and one child), four patients had complete relief with no recurrence and nineteen had partial relief with subsequent recurrences.

TABLE V. LONG-STANDING RESULTS WITH PER CENT OF RECURRENCES

GROUP	NO RECURRENCE		RECURRENCES		FAILURE	
	NO.	%	NO.	%	NO.	%
Adults (107)						
Post-status Group I (22)	4	18.2	18	81.8	0	0
Acute Group II (50)	12	24.0	35	70.0	3	6.0
Chronic Group III (35)	10	28.6	22	62.8	3	8.6
Total	26	27.3	75	70.1	6	5.6
Children and Infants (46)						
Post-status Group I (1)	0	0	1	100.0	0	0
Acute Group II (31)	17	54.8	14	45.2	0	0
Chronic Group III (14)	4	28.6	9	64.26	1	7.14
Total	21	45.6	24	52.2	1	2.2
All Groups (153)						
Post-status Group I (23)	4	17.4	19	82.6	0	0
Acute Group II (81)	29	35.8	49	60.5	3	3.7
Chronic Group III (49)	14	28.5	31	63.3	4	8.2
Total	47	30.7	99	64.7	7	4.6

In the group of patients with acute asthma, which was composed of eighty-one patients, there were fifty adults, twenty-nine children, and two infants. Of these, twenty-nine had complete relief, forty-nine had partial relief, and three showed no improvement with prednisone therapy. In the chronic group, consisting of forty-nine patients, there were thirty-five adults and fourteen children. Of this group, fourteen were completely relieved, thirty-one partially relieved, and four were failures.

Grouping the results, we note that, of all the patients, 30.7 per cent were completely relieved and were carried along on the usual allergic management without any recurrence.

Partial remission was achieved in 64.7 per cent of all groups. In this group we noted a large number who, we believed, showed evidence of "escape mechanism." When the dose of prednisone was increased or an injection of ACTH was given, a large number of these patients were then carried along on a maintenance level of prednisone, in addition to the usual allergic management. It is worth while to note that, of all the patients in our study, there were only 4.6 per cent complete failures. Therefore, with improvement from complete to partial in over 95 per cent of the patients placed on prednisone, this drug, in our experience, is one of the great advances in the armamentarium of drugs used for allergic disease, especially bronchial asthma.

Many of our patients had previous therapy with ACTH, cortisone, and hydrocortisone (Table V). These patients who had been treated with ACTH, cortisone, or hydrocortisone had no difficulty when prednisone therapy was instituted.

The most important indication for the use of antibiotics was to avoid the masking of an infection that developed during the therapeutic period or to assist the body defenses in overcoming a pre-existing infection.

From Table II, it will be noted that, of the twenty-three patients in Group I, seventeen were given antibiotics during the therapeutic period, while it was necessary to keep only three patients on antibiotics during the maintenance period.

In the chronic group, consisting of forty-nine patients, thirty-two required antibiotics during the therapeutic period and twenty-one remained on antibiotics during the maintenance period.

In this group, it will be noted from Table I, many of the patients had evidence of pre-existing chronic infections; therefore, it is not surprising that a larger per cent were placed on antibiotics and a larger per cent remained on antibiotics. The most commonly used antibiotics were Terramycin, penicillin, dihydrostreptomycin, tetracycline, and erythromycin.

We were surprised to note, in studying the reports of other investigators, the paucity in the use of antibiotic drugs or chemotherapeutic agents during the period of prednisone administration. It is our belief that the excellent results we obtained in the acute status asthmaticus and chronic bronchial asthma patients were enhanced by the use of these drugs.

From Table IV, it will be noted that we had a rather large group of side reactions. These reactions were not immediately noted, but usually developed in patients who were on the drug for at least two weeks or longer. The longer the duration of use of the drug and the larger the dose required for effective control of symptoms, the greater were the number and severity of side effects noted.

While the side effects noted in the entire group, as compared to similar patients on ACTH, cortisone, and hydrocortisone, were less severe, all those previously ascribed to the previously mentioned corticosteroids were found to be present to some degree in our study.

Other investigators have differed in their observations about the side effects of prednisone and we believe that this difference is due to the fact that their period of therapy was shorter or, if of longer duration, the dose was smaller.

Recent reports call attention to the activation of peptic ulcers in patients on prednisone, some of which perforated with dire results. In addition, the most disturbing so-called side effects are those which occur after the drug has been completely withdrawn and the patient experiences a "stress reaction." We have not actually experienced this, but evidence is beginning to appear indicating that cases of sudden death have occurred in those patients who had previously been on prednisone and were involved in an accident or were subsequently subjected to an operation requiring anesthesia, or in whom an acute infection ensued with a shocklike syndrome. Similar fatalities from cortisone, hydrocortisone, and ACTH therapy are a matter of record.

It would appear, from this evidence, that a simple test for adrenal insufficiency should be used at frequent intervals after discontinuance of prednisone or other corticosteroids in order to avoid this "escape mechanism." In our patients in which we noted the "escape mechanism," evidence of clinical adrenal suppression or atrophy could be overcome by a stimulating dose of ACTH. This emphasizes the importance of keeping the adrenal responsive by periodic administration of a long-acting ACTH.

We had some experience with the use of prednisone complicated by other diseases. In one case of bronchial asthma complicated by diabetes, the patient was able to tolerate prednisone when insulin was increased to overcome glycosuria and hyperglycemia.

In six patients with evidence of hypertension, the blood pressure was adequately controlled when a salt-free diet and the drugs belonging to the Rauwolfia group were given in addition. As a matter of fact, in some of the patients, blood pressure dropped when the asthma was controlled by prednisone.

A few patients with bronchial asthma and frank cardiac disease were treated with prednisone and improved without evidence of any increase in their cardiac symptoms. One asthma patient who had a coronary occlusion did not show any deleterious effect while on prednisone therapy. Two patients with asthma, who had previously been on cortisone and who showed evidence of pulmonary infiltration which was suspected to be tuberculosis, were placed on prednisone with no increase in the pulmonary infiltration as had been previously noted.

SUMMARY

1. Prednisone is a very effective drug in bronchial asthma, and shows marked anti-inflammatory action. In our studies it is approximately four to five times more effective, on a weight basis, than cortisone or hydrocortisone.

2. Side effects observed were those previously described with cortisone and hydrocortisone, but the dose required to produce these effects was proportionately larger and the length of time was much longer.

3. Attention is called to the serious complications of adrenal insufficiency following stress phenomena and the value of long-acting ACTH to correct or offset this complication.

4. The use of antibiotics has been pointed out as a factor in increasing the effectiveness of prednisone or ACTH in patients who show evidence of infection, and it gave more gratifying results.

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GASTROINTESTINAL WHEAT ALLERGY

Two Recent Experiences

H. J. Roberts, M.D., West Palm Beach, Fla.

THIS report has been prompted by the recent observation of two patients who demonstrated profound improvement of severe gastrointestinal disability only after a wheat-free diet had been instituted. It is presented primarily as a clinical and therapeutic study in view of the renewed interest in wheat allergy, particularly as this phenomenon relates to the sprue and celiac syndromes.

As the literature is culled for the more authoritative presentations dealing with allergy to wheat and other foodstuffs, one is impressed with the great reserve with which he is cautioned to make such a diagnosis. Most authors stress the general unreliability of skin and passive transfer tests to foods, the leukopenic index, and the other "specific" tests which have been advocated for the diagnosis of an allergic state. Enthusiasm or skepticism is held by both allergists and gastroenterologists alike for the provocative tests, the clinical observations following the use of elimination diets, the roentgenologic evaluation of the effect of barium-specific food mixtures upon the tonus, motility, and mucosal pattern of the intestinal tract, and direct studies of the local reaction to allergens either by gastroscopy or proctosigmoidoscopy. The use of control studies followed by the administration of the suspected noxious agent in a disguised form is frequently suggested.

To complicate the subject further, there are many diverse opinions relating to the actual incidence of both food and gastrointestinal allergy. As Ingelfinger, Lowell, and Franklin[1] have stated, "Gastrointestinal allergy is a diagnosis frequently entertained, occasionally evaluated and rarely established. It offers to its enthusiastic supporters a reasonable explanation for many obscure abdominal complaints." Many authors interested in the psychodynamics of food intolerances and allergy stress the psychic identification of patients to food, and the great difficulty in separating the salutary effects of the elimination diet itself, on the one hand, from the combination of dietetic ritual and the physician's interest and enthusiasm on the other. The reader is referred to the standard allergy texts and to the reviews by Tuft,[2] Andresen,[3] Schloss,[4] Rowe,[5] Ingelfinger and his associates,[1] Graham and his associates,[6] Withers,[7] Kaufman,[8] Loveless,[9] Cooke,[10] and Hill[11] for further general discussions of the problem.

Within the past five years, interest in wheat and gluten allergy has been revived. This has been due chiefly to the reports in Holland by Dicke[12] and Weijers and Van de Kamer[13] and in England by Anderson and his associates[14]

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and Sheldon and Lawson[15, 16] of the remarkable improvement noted clinically and biochemically in celiac disease when wheat and rye flour are excluded from the diet. In one study, the fecal fat content returned to normal in six out of seven children.[14] The gluten fraction apparently has been specifically incriminated, and the maintenance of a gluten-free diet is now the objective in the dietary management of these children. In fact, one company in England now separates wheat flour into its protein and starch components in the course of preparing their particular food commodities. It makes available for celiac children the whole wheat starch which, by means of special recipes, can be made into bread, biscuits, and cakes, thus taking the place of whole wheat flour. (Such special recipes are necessary because, in the absence of gluten, a wheat starch loaf would crumble to pieces unless some substitute for the binding properties of gluten were used. Its place is taken by fat and milk.)

In adults, significant wheat or gluten allergy in sprue and other gastrointestinal disorders has been given more specific consideration since the recent report by Ruffin and his colleagues.[17] The case was presented of a 39-year-old woman who experienced a clinical, biochemical, and even a radiologic remission on a wheat-free diet after sprue which had remained severe in spite of intensive treatment with folic acid, liver extract, and vitamin B_{12}. The patient with sprue herein reported confirms this observation. All the authors who have written recently on this subject imply that the beneficial effects in both sprue and celiac disease of such varied diets as the banana diet, the vegetable-fruit diet, the starch-free diet, and the many others advocated may actually be due to the absence of wheat. In his radiologic text, Golden[18] describes the striking case of a patient with the clinical and x-ray diagnosis of sprue who remained in good health on a regime of bananas, vitamin B complex, and oral liver; if he ate wheat, diarrhea would promptly ensue. Even before the modern concept of allergy existed, such instances were known to occur in both man and animals, and were diagnosed as "buckwheat poisoning."[19] Although Andresen, Rowe, Walzer, and Vaughn[20] have constantly alluded to the importance of wheat allergy in these conditions, attention heretofore has not been brought out in such clarity as to its significance.

Our unsuccessful experience with the use of cortisone prior to the institution of the wheat-free diet has raised several additional postulates in our thinking concerning the beneficial effect of cortisone, hydrocortisone, or corticotropin reported by others in the primary sprue syndrome. Since those patients who did respond to hormonal treatment uniformly relapsed one to three weeks after cessation of the steroids, notwithstanding the continued administration of liver extract, vitamin B_{12}, and folic acid, it is apparent that the explanation for this improvement must be other than one of simple replacement therapy. In view of the recent evidence demonstrating both the hydrocholeretic and true choleretic effects of cortisone,[23] it is possible that

this action may have improved the defective intestinal absorption somewhat. This seems less likely in the universally noted absence of improvement after the administration of large amounts of the bile salt preparations.

Attempts have been made to relate the etiology of the primary sprue process to adrenocortical insufficiency on the basis of the diminished fat absorption in Addison's disease, the flat oral glucose tolerance curves, the diarrhea and weight loss, and the superficial resemblance of the sprue and Addisonian patients.[24-26] Almy[27] and Paniagua and associates[28] have independently studied this problem and conclude that the adrenal cortical reserve is normal in both tropical and nontropical sprue.

It is quite possible, on the other hand, that these steroids do interfere with allergic reaction to wheat or gluten in some temporary manner which we are as yet unable to explain. This observation is enhanced by the fact that the progressive course of the sprue syndrome secondary to such diverse entities as lymphoma, amyloidosis, Whipple's disease, and extensive mesenteric tuberculosis cannot be influenced by hormonal therapy. It has even been emphasized that steroid therapy should be administered with caution in sprue. If one is not constantly aware of the fact that the steroids enhance potassium excretion and that a marked potassium deficiency may already exist, a serious hypokalemic hypochloremic alkalosis is likely to ensue.[29] Furthermore, these agents have been clearly shown to interfere with calcium therapy.[30] Consequently, their use in sprue, hypoparathyroidism, and other hypocalcemic states can readily produce clinical tetany, such as occurred in our first patient.

The specific sensitization of patients to the products of food digestion in the form of primary and secondary proteoses has been investigated intermittently for many years (Cooke,[31] Tuft and Blumstein,[32] Ancona and Schumacher,[33] Wacker and co-workers[34]). Enthusiasm for this theory waxed notably when the favorable results from the use of propeptones were reported in the treatment of gastrointestinal food hypersensitivity.[35, 36] It had recently waned with the report of Bloom, Markow, and Redner,[37] in which it was concluded that "changes in the antigenicity of foods as a result of digestion, as indicated by skin tests and intentional feeding tests, are an infrequent occurrence. In the search for the etiologic agent in nonreactive cases, the use of digest extracts for testing purposes will offer no advantage over a thorough and carefully taken history, confirmed by test feedings." In this regard, it is of interest that in the second patient here reported, with a severe gastrointestinal allergy to wheat manifested by diarrhea, a marked eosinophilia, and abdominal pain, the symptoms were experienced *only if wheat were ingested*. Exposure to wheat flour during the course of his occupation as a baker produced no symptoms, provided he maintained his wheat-free diet.

CASE REPORTS

CASE 1.—T. M. N., a 61-year-old white man, was hospitalized in June, 1954, complaining of increasing weakness, difficulty in walking, and diarrhea. He had been well until about one year previously, when typical angina pectoris was experienced along with marked weak-

ness. An examination by his family physician disclosed the presence of a macrocytic anemia. The patient was subsequently treated with vitamin B_{12} and did well for a period of six months, at which time he discontinued treatment. Several weeks thereafter, he developed stiffness of the joints, weakness, and diarrhea. His symptoms gradually increased in severity, particularly the diarrhea, which was described as consisting of from three to five loose, yellow, foul-smelling stools daily. He had lost 40 pounds in an eight-month period. Anorexia, soreness of the tongue, dysphagia, and vomiting were denied.

Physical examination disclosed a fairly well-developed but undernourished, gray-haired, blue-eyed man who appeared chronically ill. The pertinent findings were as follows: The blood pressure was 130/75. The temperature was normal. Moderate emphysema was present. The liver was palpable 5 cm. below the right costal margin; the spleen was not felt. There was a moderate dorsal kyphoscoliosis.

Laboratory and X-ray Data.—The hemoglobin was 13.8 Gm. per cent; hematocrit, 44 per cent. A white cell count was 6,200, with a normal differential count. The urinalysis and serology were negative. An iliac crest marrow aspiration revealed a mild erythroid hyperplasia. The fasting blood sugar was 90 mg. per cent. The serum albumin was 3.6 Gm. per cent, and the serum globulin was 2.3 Gm. per cent. Blood urea nitrogen was 11 mg. per cent. Stool examinations repeatedly revealed the presence of large amounts of neutral fat and fatty acid needles. The serum calcium was 5.2 mg. per cent. The alkaline phosphatase was 6 Bodansky units. A gastric analysis revealed a complete histamine achlorhydria. The oral glucose tolerance test produced a flat curve. A small bowel series showed generalized segmentation, fragmentation, thickened folds, flocculation of the barium, and the "moulage" sign. The stomach and large bowel pattern appeared normal. An x-ray examination disclosed a generalized decalcification of the bones of the spine, pelvis, and knees. Electrocardiograms revealed the presence of a right bundle branch block.

Clinical Course.—Since he had already received large amounts of vitamin B_{12}, the patient was started on cortisone acetate orally. This had to be discontinued in several days, however, because of the occurrence of carpal-pedal spasm. He was then placed on folic acid, supplementary calcium, and vitamin D. After several weeks, he still showed no improvement.

The patient was then started on a wheat-free diet. Within two weeks there not only had been profound symptomatic improvement, but his stools had become darker in color and less offensive in odor. By the time of discharge, he was having only one to two normal bowel movements daily and his serum calcium and phosphorus had both returned to normal. He was advised to remain on a wheat-free diet along with supplemental calcium. One month later, he was feeling well in all respects and was having normal bowel movements. He had gained approximately ten pounds in weight. Four months later, he was requested to return for further biochemical and x-ray studies, but he declined to do so because he felt so well. Several days after that, the patient died suddenly, presumably due to a myocardial infarction. No post-mortem examination was performed.

CASE 2.—P. D., a 53-year-old white baker, was admitted on Aug. 16, 1954, because of continuous diarrhea and weight loss for the six weeks prior to admission. There had also been associated tenesmus and urgency in the rectal area with diffuse abdominal discomfort, occasionally cramplike and most marked in the right lower quadrant. On one occasion, he had experienced a true shaking chill. He had lost approximately twenty pounds in weight during this time, which was associated with moderate anorexia. He denied ever previously having had any difficulty with his gastrointestinal tract or of having had dysentery while in the Service. Two weeks prior to admission, he was examined by a radiologist who suspected a carcinoma of the cecum because of the local discomfort and irritability observed in that area.

He had had spring hay fever at one time, but denied asthma or other significant allergic stigmata. There was no significant family history of any allergy. During the previous year, surgical treatment had been performed for bilateral varicose veins, with

an uncomplicated postoperative course. At that time, he was sigmoidoscoped for pruritus ani, which was offered as an incidental complaint; this examination was not remarkable.

Physical examination on admission revealed a well-developed and well-nourished, but somewhat pale, white man of the approximate stated age, complaining of some distress in the right lower quadrant. The vital signs were within normal limits. The significant findings were limited to the following: slight pallor of the conjunctivae; healed appendectomy and herniorrhaphy incisions bilaterally; considerable tenderness on firm palpation in the right lower quadrant area, but with no palpable masses. The rectal examination and several sigmoidoscopic examinations revealed no significant abnormalities.

Laboratory Data.—Repeated urinalyses were within normal limits. White cell counts approximated 10,000 per cubic millimeter, with the differential averaging neutrophils 26 per cent, lymphocytes 37 per cent, monocytes 3 per cent, and eosinophils 34 per cent. The latter eosinophilia was repeatedly obtained. A total eosinophil count was 3,000 per cubic millimeter. Hemoglobin 14.2 Gm. per cent. Hematocrit 45 per cent. His serology was repeatedly negative. Nine stool examinations, freshly passed and carefully examined, were negative for blood, ova, and parasites. Thymol turbidity was 7 units. Total protein was 6.9 Gm. per cent, with an albumin/globulin ratio of 4.9/2.0. Cephalin flocculation was 3+ at forty-eight hours. Stool cultures were repeatedly negative for the enteric pathogens. The remaining liver function tests, including a forty-five-minute bromsulphalein retention, were within normal limits. A bone marrow examination revealed some hyperplasia of the bone marrow, particularly of the eosinophilic myeloid elements; no neoplastic cells were noted. A trichinella skin test was negative. The electrocardiogram was within normal limits on two occasions.

X-ray Data.—Calcifications were seen in the left hilar area and left upper lung field, representing a calcified primary complex which had not changed over several years. Two upper gastrointestinal series, with particular attention focused upon the small bowel, and three barium enemas at intervals of three weeks were all within normal limits. An intravenous pyelogram was interpreted as normal.

Clinical Course.—In view of the patient's age, the recent history of a profound change in bowel habits, and the presumed disease previously noted by the radiologist, he was initially considered to have a carcinoma of the cecal area. The diarrhea persisted, with five to ten brown, semiformed stools daily. His lower abdominal distress also persisted, but he remained afebrile throughout the entire period of his hospitalization. After repeated sigmoidoscopic and gastrointestinal x-ray studies revealed no overt pathology, other diagnoses were considered. These included amebiasis with possible liver involvement, the collagen disorders (lupus erythematosus disseminata, polyarteritis nodosa), trichiniasis, atypical infectious hepatitis or infectious mononucleosis, Whipple's disease and, by exclusion, a gastrointestinal allergy. The diagnoses of pancreatitis and retroperitoneal lymphoma were also considered, but there was no evidence to support these.

In view of the repeated normal bowel studies by both x-ray and proctosigmoidoscopy, the persistent absence of any forms of *Endamoeba histolytica,* the absence of heterophile agglutinins, and the negative trichinella skin test, these diagnoses were also eliminated. In addition to the normal liver function studies, a liver biopsy was performed which was within normal limits; special stains failed to reveal either iron, parasites, or the presence of tumor cells. A second-strength tuberculin test was negative at five days. The gastrocnemius muscle was biopsied (in the absence of any macroscopic nodules); no evidence of any inflammation or parasites could be found.

The patient's history was accordingly intensively reviewed for the possibility of a food or drug allergy. In regard to the latter, he had taken no medication of any nature of which he was aware. He did recall, however, that many years previously when he initially went into baking, he had experienced "baker's asthma" for a brief period. He had always been a well-adjusted family man. A detailed psychological investigation yielded no pertinent information.

Since the number of daily bowel movements had gradually decreased to three, he was placed on a *provocative* allergic diet, consisting of wheat, eggs, milk, and oranges. Shortly after this regime had been instituted, he began to experience a marked exacerbation of his diarrhea along with the right lower quadrant pain and frequent headaches. The addition of Pyribenzamine in adequate dosage had no effect on either these complaints or on his eosinophilia. The patient was then placed on a special allergic *elimination* diet, consisting primarily of rice and rice products, peas, a gelatin drink, raspberries and Jello (modified after Andresen[3]). On this regime, while keeping a careful diary as to both his complaints and the number of bowel movements daily, the latter decreased to either none or one to two, and were normal in appearance. Once this base line had been reached, additional foodstuffs were gradually added as follows: milk, eggs, oranges, other fruit juices, and finally wheat. He had no difficulty until wheat was added, following which he again began to experience up to seven bowel movements daily, along with his abdominal distress. At no time was there any rise in body temperature. The patient was then placed on a strict wheat-free diet, on which he again experienced a complete clinical remission. During this stage, he was skin tested to various foods, including the available wheat preparations, but no positive skin reactions were demonstrated. It was the opinion of the consultant gastroenterologist that there was no evidence to incriminate any other intestinal disorder; it was the opinion of the consultant allergist that the diagnosis of a food allergy, probably to wheat, was justified.

In view of the fact that the patient had been trained only as a baker, during which work he was constantly exposed to the inhalation of wheat flour, the proper advice concerning his occupation was quite problematic. After thorough deliberation of the subject, particularly with the possibility that he might only be sensitive to a breakdown product of the wheat in his intestinal tract, he was allowed to return to work on a trial basis. After three months of careful observation following the resumption of his occupation and while on a wheat-free diet, he remained completely symptom-free. Several blood counts done in the interim revealed an eosinophilia ranging from 0 to 3 per cent on smear. At the end of the three-month period of observation as an outpatient, the patient was subjected to repeat intestinal x-rays; these again were within normal limits. He admitted that he was now able to tolerate very small amounts of wheat without symptoms; however, the occasional ingestion of any larger amounts would produce distress.

CONCLUSION

The issues of gastrointestinal and wheat allergy have been reviewed as they pertain to the recent literature.

Prompt remissions were observed in two patients treated with wheat-free diets. Their cases are herein reported.

In Case 1, severe primary sprue had been present which had become refractory to vitamin B_{12}, folic acid, and cortisone acetate. After the institution of this dietary regime, the patient remained symptom-free. Both his hypocalcemia and steatorrhea had reverted to normal one month after the diet had been started.

The temporary beneficial effects of steroid therapy previously noted in sprue may be ascribed to the interference with this hypersensitivity state.

The other patient exhibited a severe gastrointestinal allergy to wheat manifested by diarrhea, a marked eosinophilia, and abdominal pain. A complete clinical and hematologic remission was also experienced on a wheat-free diet, even though he was exposed to wheat flour dust during the course of his occupation as a baker. A specific sensitization to gluten or another of the products of wheat digestion has been inferred.

I am indebted to Dr. Alton Paull for furnishing many of the details pertaining to the first case.

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AIR-BORNE MOLDS IN HONOLULU

W. A. Myers, M.D., Honolulu, Hawaii

THE primary purpose of this survey was to compare counts of air-borne mold spores in Honolulu with similar surveys in mainland cities.[7] In this way, we hoped to be able to evaluate better the relative importance of this factor on the incidence of respiratory allergy in Hawaii. In addition to this, we attempted to evaluate various factors that may influence the spore counts.

METHOD

Standard-sized (9 cm. in diameter) Petri dishes containing medium recommended by the Subcommittee on Mold Survey of the American Academy of Allergy[1, 7, 9] were exposed for twelve minutes at about noon on the balcony of the second floor of our clinic building in Honolulu. The colonies were identified and counted four or five days after exposure by two members of our laboratory staff.

A total of 248 plates were exposed over a period of sixteen months. Total colonies counted were 1,803. We believe that the data from the last six months of the survey are the most accurate because of experience gained in identification of colonies during the first few months, so data from these months, totaling 139 plates and 1,273 colonies, are used in this discussion, except in Fig. 1. Daily counts were made during this time, except for week ends.

Fifteen different genera were identified, as shown in Table I. These corresponded fairly closely with a survey reported by Halde[6] in 1950. However, we did not attempt to identify the relatively uncommon types. It will be noted that Alternaria, which along with Hormodendrum is the most common mold spore found in many mainland surveys, is seldom found here.[2, 3, 5, 7-9, 11]

The percentage of the more common spore colonies to the total count is shown in Table I. This table also shows the average number of colonies per plate for the survey and the range of the monthly averages of colonies per plate from the lowest to the highest monthly average.

Table II shows that Honolulu has lower monthly average plate counts and also lower peak counts, than most of the mainland cities for both Hormodendrum and Alternaria and for total spore counts.

It was found that over a period of sixteen months the monthly spore counts of Hormodendrum (comprising one-third of the total spore counts) and the total monthly spore count formed parallel graphs.

As seen in Fig. 1, the average spore count per plate per month does not vary a great deal from month to month, but tends to be slightly higher in the

From the Department of Pediatrics, Straub Clinic, Honolulu, Hawaii.
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TABLE I. FUNGI ISOLATED FROM 139 PLATES EXPOSED IN HONOLULU DURING SIX MONTHS OF 1953

COLONY	TOTAL COUNT	PER CENT OF TOTAL	AVERAGE PER PLATE	EXTREMES OF AVERAGE OF COLONIES PER PLATE PER MONTH	
				LOW	HIGH
Hormodendrum	430	33.5	3.1	0.8	6.5
Aspergillus	134	10.0	0.9	0.4	1.6
Monilia	110	9.0	0.8	0.0	1.3
Penicillin	83	7.0	0.6	0.3	1.2
Fusarium	71	6.0	0.5	0.2	1.0
Mycelia Ster.	35	3.0	0.3	—	—
Torula	24	2.0	0.2	—	—
Yeast	13	1.0	0.1	—	—
Paecilomyces	11	—	—	—	—
Alternaria	10	—	—	—	—
Pullularia	9	—	—	—	—
Oospora	4	—	—	—	—
Helminthosporium	1	—	—	—	—
Rhizopus	1	—	—	—	—
Others	3	—	—	—	—
Unidentified	340	27	2.4	—	—

TABLE II. AVERAGE NUMBER OF MOLD COLONIES PER PLATE AS FOUND IN HONOLULU COMPARED WITH SOME MAINLAND CENTERS

CENTER	HORMODENDRUM		ALTERNARIA AVERAGE FOR 6 MOS.	TOTAL MOLD COUNTS AVERAGE FOR 6 MOS.
	AVERAGE FOR 6 MOS.	HIGHEST MONTHLY AVERAGE		
Honolulu, Hawaii	3.6	6.3 (Aug.)	0.07	9.55
Des Moines, Iowa	21.0	33.3 (Aug.)	11.0	60.0
Los Angeles, Calif.	19.6	33.0 (May)	5.30	40.0
Madison, Wis.	19.6	43.3 (Oct.)	18.9	50.0
Santa Barbara, Calif.	7.3	11.2 (May)	2.50	18.0
San Diego, Calif.	7.1	11.0 (May)	1.12	21.0
Oklahoma City, Okla.	7.0	15.6 (May)	10.7	27.2
Ann Arbor, Mich.	3.7	7.8 (Sept.)	10.7	28.8
Richmond, Va.	2.4	3.8 (Sept.)	7.1	27.0
Oakland, Calif.	1.5	5.0 (Oct.)	0.37	6.0
Chicago, Ill.	0.3	3.0 (Oct.)	18.0	?
Tucson, Ariz.	0.1	0.6 (Sept.)	1 0	11.0

TABLE III. INFLUENCE OF LOCAL WIND VELOCITY ON SPORE COUNTS

MONTH	WINDY		NORMAL BREEZE		CALM	
	NO. DAYS	AVERAGE COUNT	NO. DAYS	AVERAGE COUNT	NO. DAYS	AVERAGE COUNT
November	4	4.7	8	11.0	11	4.5
December	4	42.7	10	9.0	14	7.0
January	3	24.0	14	10.7	8	8.0
Total	11	71.4	32	30.7	33	19.5

TABLE IV. COMPARISON OF THE EFFECT OF PREVAILING "KONA" (SOUTH) AND TRADE (NORTHEAST) WINDS ON THE SPORE COUNTS

"KONA" WINDS		"TRADE" WINDS	
BREEZY	CALM	BREEZY	CALM
12.6	7.0	12.9	4.3
Total 19.6		Total 17.2	

winter months. According to Alvarez and Castro,[1] this is also true in Havana, Cuba. This curve did not seem to correlate with monthly precipitation, absolute humidity, direction of prevailing winds or the temperature, as reported by the local weather bureau.

A comparison of the monthly incidence of onset of attacks of asthma seen in our pediatric department[10] and the monthly total spore counts did not seem to be related in 1953, as shown in Fig. 1. Apparently the most important factor in the individual plate counts was the amount of local wind at the time the plates were exposed, as shown in Table III. This was also found to be true in several other similar surveys on the mainland and in Cuba.[1-3] (*Note:* A notation was made of the wind velocity and direction at the time the plates were exposed during November, December, and January, 1953-54.)

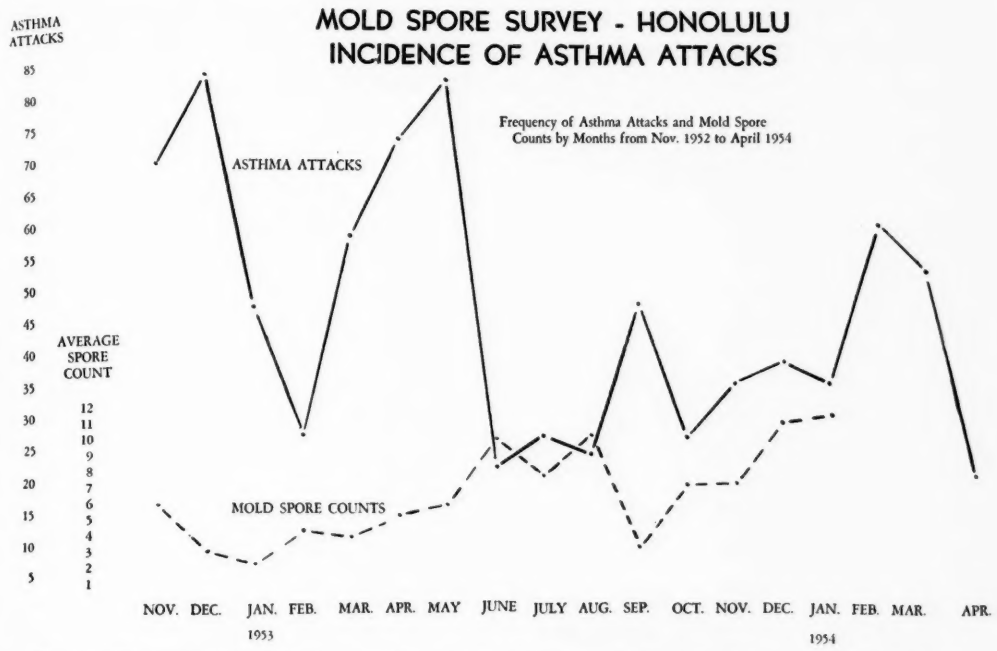

Fig. 1.—The monthly incidence of attacks of asthma in children seen by us in Honolulu as compared with the average spore counts per plate for each month.

Table IV compares the spore counts with regard to the wind direction and velocity at the time of exposure. During December and January, the direction of the prevailing wind was noted at the time of exposure of the plates. It will be noted that the wind direction had little or no influence on the spore counts at this location in Honolulu (one mile north of the coast and one mile south of the mountains in central Honolulu.)[10]

In 1952, Alvarez and Castro[1] pointed out the importance of wind velocity as a factor in evaluating spore counts in the air, and described a method of reducing this factor to a minimum by counting the spores in a constant volume of stationary air within an enclosed cabinet.

TABLE V. THE AVERAGE NUMBER OF MOLD COLONIES PER PLATE OBTAINED AT VARIOUS TIMES OF THE DAY BY THE "AIR SAMPLER," IN HONOLULU

	A.M.		P.M.	
	12 TO 6 2400 TO 0600	6 TO 12 0600 TO 1200	12 TO 6 1200 TO 1800	6 TO 12 1800 TO 2400
Samples	8	18	13	49
Colonies	55	49	39	178
Average number per plate	6.8	2.7	3.0	3.6
Colonies per cubic millimeter of air	1,782	707	785	943

We used this method of collecting mold spores in the air at various times of the day, as in the similar study made by Alvarez and Castro[1] in Havana. As shown in Fig. 2 and Table V, the peak average number of colonies per plate was at about 0300 (3:00 A.M.). The counts in Honolulu were much lower and the difference between day and night counts was much less than in Havana.

AVERAGE SPORE COUNTS AT VARIOUS TIMES OF DAY IN HAVANA AND IN HONOLULU

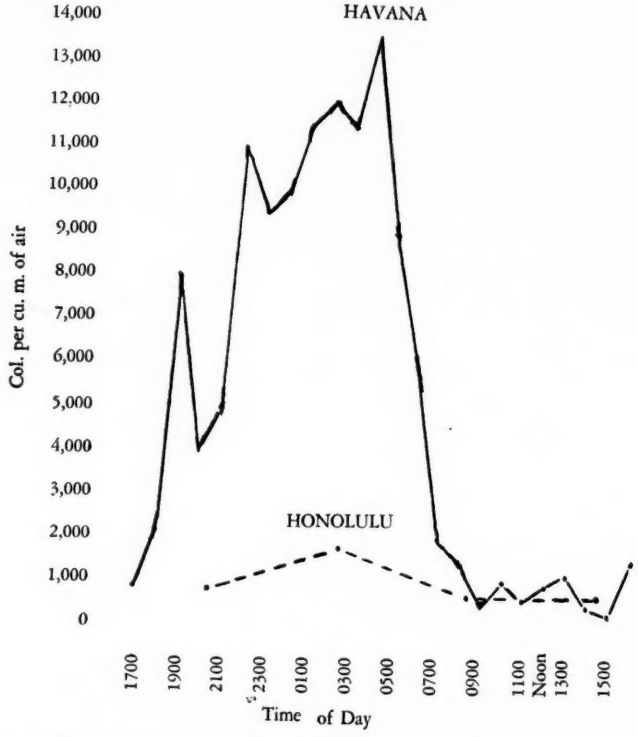

Fig. 2.—A comparison of the average spore counts per cubic meter of air at various times of the day in Havana and Honolulu. This method of sampling minimizes the effect of wind velocity on the mold spore counts.

SUMMARY

1. Mold spore counts in Honolulu are much lower than in most mainland cities.

2. Hormodendrum comprises 33 per cent and Alternaria less than 1 per cent of the total count.

3. The average monthly plate count does not seem to be correlated with the incidence of asthma in children.

4. Spore counts tend to be higher on windy days than on calm days, in spite of the direction of the wind.

5. A method of minimizing the effect of wind on spore counts by the use of an "air sampler," as described by Alvarez, was found to be fairly satisfactory.

I wish to thank Mr. Kaname Saito and Miss Gertrude Ching, of our laboratory staff, for their help in making this survey possible.

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CANKER SORES FROM ALLERGY TO WEAK ORGANIC ACIDS (CITRIC AND ACETIC)

Case Report and Clinical Study

Louis Tuft, M.D., and L. N. Ettelson, M.D., Philadelphia, Pa.

ALLERGY to foods manifests itself in different ways and can give rise to a host of clinical manifestations. The etiological relationship between the latter and the food allergy may be definite in some instances, as for example, the development of angioedema of the lip and/or asthma following the ingestion of egg by an egg-sensitive child. That egg is responsible is indicated not only by the clinical history, but by the finding of a positive skin test reaction to egg and by the presence of circulating antibodies (reagins) to egg. Whenever it is possible to obtain such confirmatory evidence, the etiological association between the offending food and the clinical condition is easy to prove. But, unfortunately, this is not true of all the clinical manifestations ascribed to food allergy, especially if the skin test reaction to the suspected agent is negative. Under those circumstances, proof of an etiological relationship must depend entirely upon the subjective clinical data supplied by the patient after the offending food or foods are eliminated while on special or trial diets. One explanation offered for the occurrence of a negative skin test reaction to the food despite positive clinical tests is that the allergy exists to a split product of the protein (for example, amino acids, as in the case previously reported by us[1]), or to an enzyme (for example, that present in raw fruits or melons[2]), or to some other as yet undiscovered agent which does not give positive skin test reactions.

Recently, we saw a patient in whom recurrent outbreaks of canker sores, ascribed at times to food allergy, seemed to be associated with an abnormal reaction or allergy to weak organic acids like citric and acetic, as indicated by the results of our clinical studies. Since we could find no record in the literature of the demonstration of a similar etiological association, it seemed worth while to report this case history and the results of our clinical investigations.

CASE REPORT

A man, aged 37 years, an Army veteran, was first seen in the Outpatient Allergy Clinic of the Veterans Administration in May, 1953, complaining of nasal blockage, asthma, and headaches. These symptoms had begun at the age of 5, following an attack of whooping cough, and had been recurring since then. Little improvement was noted either after a tonsillectomy and adenoidectomy at the age of 7 or after a submucous resection done at the age of 19.

From the Allergy Clinics, Veterans Administration Regional Office No. 10, and Temple University Hospital and School of Medicine, Philadelphia, Pennsylvania.

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The patient enlisted in the United States Air Force in January, 1942. He noted some increase in symptoms during his period of training and while flying planes in the China-Burma-India theater, especially as the result of changes in temperature as well as from exposure to the inhalation of soft coal smoke in southern Illinois and to volcanic dust in the Aleutians. In 1950, while in Texas and because of the persistence of symptoms, he was sent to the Brooks General Hospital for allergy investigation. Positive skin test reactions were obtained to milk and to a few other foods; also to dust, feathers, pyrethrum, and ragweed. Because of the recurrence of more severe symptoms of asthma and migraine headaches, he was sent to the Lackland Base Hospital where desensitizing injections of dust and ragweed pollen extracts were given for more than a year. Following this treatment, he noted fewer nasal and bronchial symptoms during the ragweed season, but continued to have headaches when exposed to dust or after the ingestion of certain foods, such as milk or chocolate.

For many years, probably since early childhood, the patient had frequent canker sores in the mouth. These were sometimes associated with headaches and also with vague muscular pains and varying degrees of lassitude. The canker sores persisted throughout his army life and up to the time he was first seen in our clinic. Having had them for so many years, he never complained about them and regarded them as trivial.

The patient remained in the Air Force until May, 1952, when he was discharged. In September, 1953, he enrolled at the University of Pennsylvania, in the Liberal Arts College, majoring first in psychology and later in sociology. Because of the continuance of the asthma, rhinitis, and headaches, he applied for treatment at the Philadelphia Allergy Clinic of the Veterans Administration. Complete intracutaneous skin tests revealed significant positive reactions to house dust, ragweed, timothy, and plantain, with negative reactions to the commonly eaten foods including milk and chocolate.

Treatment was begun shortly afterward. It consisted of the elimination of test-positive allergens and of desensitization with extracts of timothy and ragweed pollens and of house dust. The desensitizing injections still are being continued. The patient reports definite improvement in his nasal symptoms and in his asthma. The latter now is quite mild and is readily controlled by symptomatic measures (for instance, Tedral). Despite the institution of allergy treatment, the patient continued to have recurrent canker sores and headaches; also frequent spells of general lassitude, vague pains, irritability, and inability to concentrate, which interfered considerably with his studies. Because of these symptoms, he consulted the psychiatrist at the Veterans Clinic, who considered the symptoms functional in origin.

In attempting to correlate his symptoms with the offending allergen, the patient reported that exposure to smoke or dust of any type would induce severe nasal blockage and wheezing; ingestion of chocolate, candy, beer, nuts, and seafood also would cause nasal symptoms and, at times, asthma. Of particular interest in relation to our subsequent studies was his observation that the eating of chocolate (to which he had a negative intracutaneous skin test reaction) would provoke an outbreak of "sore spots" or canker sores in the mouth associated at times with "itchy bumps" on the scalp. The patient was quite accustomed to these canker sores, and for years had attributed them to the ingestion of sugars, sweets, "acid foods," or certain alcoholic drinks. The effect of the latter was verified by one episode recalled by the patient which took place during his tour of duty in Asia and which is of special interest in view of our subsequent clinical studies. Upon returning to the home base after a long tour of flying, the flight medical officer usually advised the pilots to take a few drinks to ease the tension and relieve the customary headaches which followed most flights. When the patient tried this, he usually developed migraine headaches, asthma, and canker sores. These symptoms at times were so severe that he could not report for duty, and he therefore seldom drank. He recalled that whenever he took mixed drinks containing fruit juices, he invariably developed symptoms; on the other hand, when he drank straight liquor, he might develop nausea associated with a mild "hangover," but would seldom get asthma, nasal blockage, or canker sores. The reasons for this difference will be evident later.

One of us (L. T.) saw the patient for the first time in May, 1954, in consultation. In reviewing the history with the patient, it seemed likely that the canker sores followed the ingestion of certain foods, especially grapes or anything made from grapes (for example, grape juice, jelly, wine, brandy); also, after eating chocolates and certain kinds of candies and carbonated beverages. To verify this possibility, we undertook further clinical studies and were fortunate in having the complete cooperation and exceptional assistance of a highly intelligent patient.

Clinical Studies.—A survey of the ingestants known clinically to produce his mouth symptoms indicated that one common factor nearly always was present, namely, citric acid. This substance was present either as a naturally occurring organic acid, as in citrus fruit, or it was used as an ingredient in the manufacture of commercially prepared products, as in carbonated beverages. The possibility that an organic acid such as citric acid could act as an allergen or could act as a mucous membrane irritant had never occurred to us and has not been noted in the allergy literature. Our attention to citric acid was drawn especially by some observations of this patient after a rather accidental experience.

Fig. 1.

Because of the restriction in diet, especially of milk, the patient felt weak and began to eat candy bars. This only seemed to make him worse. It induced heartburn, epigastric discomfort, gas, headache, canker sores, and general lassitude, and made concentration difficult. He attributed this to the chocolate and excess sugar and so tried other candies.

He began eating Necco wafers, especially while in class, and would take one of the wafers from the package in his pocket and slip it into his mouth without seeing it. He reported that certain wafers seemed to cause a puckering or itching sensation in the mouth and peculiar discomfort in the stomach. Upon further investigation, he noted that this would happen after eating yellow, green, or orange wafers which apparently contained citric acid, but not from the white, cinnamon, or even the chocolate-flavored ones, presumably those without citric acid. To eliminate the possibility that sugar was responsible, he ate pure cane sugar cubes and also rock candy without difficulty. Since he could take the chocolate wafer without trouble, he tried eating the pure chocolate which

is used by confectioners or bakers in preparing candy or pastry. This caused no symptoms, whereas most of the commercial chocolate bars, which according to the labels contained citric acid, induced canker sores.

This seemed to indicate that the patient was not allergic to chocolate itself but to substances combined with it. As a result of these experiences, the patient became quite adept at determining whether anything he ate or drank contained citric acid. Thus, for example, he found that he could not tolerate certain cough drops or troches (such as the red-colored Smith Brothers), whereas others were all right. This also was true of certain beverages; for example, he could drink unlimited amounts of Hires Root Beer (which, according to the label, does not contain citric acid) without symptoms, whereas one Coca-Cola or even club soda (both of which do contain citric acid) induced canker sores. As a result of these experiences, the patient became label conscious, inspecting all labels for citric acid and avoiding foods containing it. By strictly avoiding all substances containing citric acid, the patient could remain relatively free of canker sores for long periods and also could induce the sores at will by eating citric acid-containing foods.

Because of our suspicion that citric acid was the culprit, we coincidently began a series of investigations designed to determine whether our clinical suspicions could be verified. Since substances like citric acid do not give positive skin test reactions even in sensitive patients, we felt that there was a better chance of verification if we used a direct mucosal contact test. Accordingly, we had the patient put a small crystal of citric acid (contained in sour salt) into the oral cavity in the space formed by the lower lip and the lower anterior alveolar surface. Within a few hours, there was a reddening and edema at this area. By the next day a white, raised patch 12 to 18 mm. in diameter was present, with two or three papular elevations around its border. The area sloughed away leaving a craterlike ulcer with slightly raised edges (Fig. 1). Following the healing of this ulcer, which required about ten days, the patient then repeated the test in a different area, leaving the crystal in contact for fifteen seconds. Again the same chain of events occurred at the contact point, but a smaller area was involved. By later tests, it was found that even momentary contact of a citric acid crystal on the oral membranes was sufficient to produce canker sores. Control tests with potassium citrate crystals were negative, and tests with citric acid crystals upon members of the patient's family and many other individuals were negative. We then tried other related substances, or those containing citrate, with results shown in Table I. All the substances tested were in the form of crystals except magnesium citrate, which was in liquid form. The latter was tested by moistening a pledget of cotton with the solution and placing it in the oral cavity in the same manner as the crystals.

TABLE I. RESULTS OF MUCOSAL CONTACT TESTS WITH CITRIC ACID AND RELATED SUBSTANCES

SUBSTANCE	RESULT OF CONTACT TEST
Citric acid (sour salt)	Strongly positive
Potassium citrate	Negative
Magnesium citrate (solution)	Negative
Alka-Seltzer (citric acid, aspirin, sodium bicarbonate)	Moderately positive
Aspirin	Negative
Sodium bicarbonate	Negative
Bromo-Seltzer (citric acid, acetanilid, caffeine, sodium bicarbonate, sodium bromide)	Negative

It will be observed from Table I that all the compounds containing free citric acid gave positive mucosal tests with the exception of Bromo-Seltzer. The negative test to the latter perhaps can be explained by the fact that the citric acid in Bromo-Seltzer, when dissolved, quickly changes to sodium citrate. It is noteworthy that when the patient was

testing it, he noticed that when he placed the crystal against the oral mucosa it dissolved quickly in comparison with Alka-Seltzer crystals which remained in solid form much longer.

While it seemed evident from the results of our contact tests that citric acid was responsible for the canker sores in the clinical experiments, a question arose as to whether it was a matter of pH; also, even though the resultant ulcers were seen by one or both of us after the completion of some of the tests, observations of the patient himself had to be taken in reporting the results of most tests. To check this, blind mucosal tests were done by the patient with two solutions prepared by Dr. Hamilton* and marked "A" and "B." The patient was instructed to test the solutions by means of pledgets of cotton moistened in the solution and applied to the oral mucosa for a period of three minutes in the first test, and fifteen minutes in the later one. Different mucosal areas were used each time and sufficient time was allowed to elapse to permit the ensuing reaction to diminish. Solution "A" produced negative results both times. Solution "B", after three minutes, produced a definite positive reaction in the form of a red patch; after fifteen minutes, a much larger area of redness was noted, although no ulcer formed, probably because of the weak concentration used. Following the completion of these tests, we were told by Dr. Hamilton that Solution "A" was a weak solution of HCl (tenth normal), whereas Solution "B" was a weak solution (about 2.5 per cent) of citric acid in corresponding pH. These experiments, therefore, seemed to confirm the previous observations that citric acid was the specific offending agent, rather than the "acidity" or the irritative qualities of an acid substance.

TABLE II. RESULTS OF MUCOSAL CONTACT TESTS WITH ORGANIC ACIDS

SUBSTANCE	RESULT OF CONTACT TEST
Tartaric acid	Mildly positive
Acetic acid (apple vinegar)	Strongly positive
Lactic acid	Mildly positive
Uric acid	Negative
Ascorbic acid	Negative
Nicotinic acid	Negative
Benzoic acid (1%)	Negative

The question next arose as to whether other organic acids might act in a similar fashion to citric acid. After consultation with Dr. Hamilton, a series of mucosal tests, done either with the pure crystals or with a solution soaked in a cotton pledget, were carried out by the patient with those organic acids most frequently found in the human diet. The results of these tests are summarized in Table II.

The marked positive mucosal reaction to the application of acetic acid was surprising. But, at the same time, it explained why the patient had mouth ulcers and gastrointestinal symptoms after eating foods containing vinegar; thus, for example, the patient reported that he would develop a typical right-sided migraine headache as well as canker sores and itching of the skin after eating foods containing vinegar, such as cole slaw, potato salad, or beef cooked in vinegar, whereas he could eat plain beef with impunity. These symptoms were similar to those he noted after taking foods with excess citric acid (for example, fruit juice) but seemed more intense perhaps because he took larger amounts.

Another question presenting itself for further investigation was whether the organic acids, like citric acid, acted by direct contact with the buccal mucosa or after ingestion or by both means. To determine this, the patient took a 3 grain (0.2 Gm.) capsule (washed beforehand) of citric acid shortly after breakfast. He had no immediate reaction; but several hours later noted a gnawing pain in the epigastrium, mild diarrhea, and

*The authors are greatly indebted to Robert H. Hamilton, M.D., Professor of Biochemistry, Temple University School of Medicine, Philadelphia, Pennsylvania, for his invaluable advice and assistance in carrying out some of the biochemical studies and for some of the material employed in the tests.

slightly irritated tongue. A month later (December, 1954), he took a 5 grain (0.3 Gm.) capsule of citric acid after each of his three meals for two days, but noticed no untoward effects. Despite these results, the patient observed that ingestion of foods containing excess citric acid (fruit juices or wine) produced not only canker sores but at times inflamed furuncle-like lesions usually in the nares and less commonly in the lower lid (resembling a stye), mostly on the right side. This would seem to indicate that the organic acids act not only after direct contact but also after getting into the stomach and intestines, depending upon the amount ingested and the amount absorbed into the circulation.

Further clinical trials were made with other foods, especially fresh fruits, to determine whether they would induce the formation of canker sores. As a result of these tests, it was determined that canker sores could be provoked not only by commercial foods or drugs containing citric or acetic acids but also after the ingestion of the following foods: oranges, grapes, dried apricots, raw and canned peaches, pineapple, wines especially Chianti, brandies, beer, and most mixed alcoholic drinks. On the other hand, he determined that he could eat with impunity the following: raw or cooked apple, raw or canned pears, canteloupe, watermelon, honeydew melon, Persian melon, and raw celery; however, canned celery juice caused a puckering sensation in his mouth, perhaps because of the added preservative. While most of the reacting foods induced canker sore formation, this was not true of all of them. Thus, ingestion of milk or cheese precipitated headache, malaise, and wheezing, but no canker sores.

Following the diagnostic study and especially after extensive clinical trials which revealed the offending agents, the patient eliminated as far as possible all offending foods as well as those containing citric acids or acetic acids. As a consequence, he has noticed definite lessening of his allergic symptoms except when he inadvertently or consciously is indiscreet in his diet; if so, he can easily detect the cause of his symptoms in retrospect; or if it is a canned food, he later finds that the food contained citric acid of which he previously was unaware. He also has noted definite improvement in his general physical and mental condition, especially in his power of concentration and in a lessening of his previous irritability. The latter condition was the basis for his periodic visits to the Clinic psychiatrist for two years, but he noted no beneficial effect upon his symptoms until after the offending foods were eliminated. He now sees the Clinic psychotherapeutist (psychologist) periodically for assistance in his school problems.

COMMENT

The clinical study of this patient has revealed many interesting features which might find application to other similar patients. In the first place, it was demonstrated that the patient had a definitely abnormal reaction or allergy to citric acid and to foods or drugs containing it. This reaction took the form of canker sores proved by direct mucosal contact tests with citric acid in this patient, whereas the same agent in other control patients gave negative reactions. Similar abnormal reactions were observed from other organic acids, notably acetic acid. One might question the use of the term *allergy* to designate a reaction to nonantigenic substances like citric or acetic acids, but similar abnormal reactions designated *allergic* occur in relation to various nonprotein agents (for instance, drugs) which likewise give neither a positive skin test reaction nor demonstrable antibody. Regardless of the designation, our demonstration in this patient, apparently for the first time, of an allergy to weak organic acids is of great importance in food allergy. It is another link in the chain of evidence indicating that allergic reactions to foods need not necessarily occur in relation to the protein component but may take place in relation to the split products like peptones and amino acids, or

preformed weak organic acids, and possibly to organic acids formed from substances in food other than proteins. Such patients may have negative skin test reactions to the parent food and yet possess an allergy (of the nonatopic type) to one of its products. This helps to explain those instances where the patient has a clinical allergy to a food and yet gives a negative skin test reaction to its extract. Another interesting feature in this patient is the fact that we were able to prove by direct mucosal tests that the canker sores were caused by the abnormal reaction to the weak organic acids. Similar testing with citric acid crystals and/or a weak solution of acetic acid might be carried out in those allergic patients in whom food allergy is suspected but the skin test reactions are negative, as for example in patients with canker sores.

Despite the clinical demonstration in this patient that contact with weak organic acids induced the formation of canker sores, the manner by which this is brought about raises many unexplained questions. First is the matter of specificity. Thus, canker sores were produced in this patient not only by citric acid but also by acetic acid and, to a mild degree, by tartaric and lactic acids. Likewise, it is not easy to explain, for example, why the canker sores were induced by contact with citric acid but not from sodium citrate. The evidence needed to answer these questions involve such matters as pH, concentration, solubility, or the buffer powers of organic acids compared with that of weak HCl and can be furnished only by further experimental investigation which is now in progress.

The fact that canker sores in this patient were proved to be due to allergy to citric acid and acetic acids is of interest also because of the popular custom of physicians and patients to attribute these canker sores to an excessive ingestion of "acid foods," especially fruit juices. Suspicion of an etiological relationship could not always be verified, except for a lessened tendency for the ulcers to develop when the suspected foods were eliminated. Our investigations furnish greater support to what previously seemed like mere suspicion and indicates that "acid foods" actually can have a causal relationship. They also explain the tendency of the patient to get canker sores when he drank mixed drinks containing fruit juices and not from straight liquors.

Finally, the clinical history in this patient demonstrates that symptoms regarded as functional or psychosomatic sometimes may be due to an unsuspected or unproved food allergy. Thus, in the case herein reported, symptoms of "toxemia," including headache, muscular neuralgic pains, lassitude, irritability, and inability to concentrate, improved considerably after the elimination of the offending foods, including those containing citric acid and acetic acid, and reappeared after their readdition. This is not new, for Rowe,[3] many years ago, included these symptoms in a syndrome designated by him as "allergic toxemia," but its existence in some patients sometimes is forgotten in our present emphasis upon functional causes.

SUMMARY

A report has been made of a male patient, aged 37, treated for nasal allergy, asthma, and migraine who for years was subject to frequent outbreaks

of oral canker sores. Clinical investigation indicated that the latter usually followed the ingestion of foods, drugs, or carbonated beverages containing citric acid. Direct application of citric acid crystals to the oral mucosa repeatedly reproduced the ulcer in the patient, but not in the controls. Mucous membrane contact tests with substances containing citric acid gave similar positive results; likewise, tests with other weak organic acids contained in foods gave positive reactions to some of these, especially to acetic acid. Avoidance of foods containing the positive reactors was followed by marked relief not only of the ulcers but also of the general "toxic" symptoms previously regarded as functional. This demonstration of possible allergic reactions to weak organic acids in foods provides additional explanation for the existence of clinical allergy to certain foods in some patients despite the presence of a negative skin test reaction.

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ANAPHYLACTOID REACTION FOLLOWING THE ORAL ADMINISTRATION OF IODIDE-CONTAINING CHOLECYSTOGRAPHIC MEDIA

SHELDON G. COHEN, M.D.,* ROBERT N. ARMEN, M.D.,** AND MILTON KANTOR, M.D., WILKES-BARRE, PA.

INTRODUCTION

THE etiological role of iodine in hypersensitivity reactions has been repeatedly demonstrated so that it is not unusual to see allergic symptoms develop following the administration of iodide-containing radiographic contrast media to a patient later proved to be sensitive to this radical. The literature pertaining to this subject has been recently summarized in a comprehensive review by Alexander.[1] Dermatologic eruptions and minor allergic symptoms such as pruritus, flushing, sneezing, and urticaria are the usual clinical manifestations noted in iodide sensitivity[1, 2] reactions following intravenously administered contrast media for pyelography and the intratracheal introduction of iodized oil for bronchography. However, fatal reactions of the delayed type, attributed to renal damage[3] and those of an acute anaphylactic type characterized by the sudden onset of flushing, sneezing, urticaria, cough, dyspnea, syncope, and shock and occasionally progressing to a fatal termination,[1, 3-5] have been reported with these diagnostic procedures.

A review of the literature pertaining to oral cholecystography revealed that side reactions such as burning sensations of the throat, dysuria, diarrhea, abdominal cramps, headache, nausea, and dizziness, are occasionally seen and that only minor allergic pnenomena, such as urticaria, have rarely occurred.[6-8] However, to the best of our knowledge, there have been no instances reported of the immediate severe allergic- or anaphylactic-type reactions following the oral ingestion of iodide containing cholecystographic media. Recent experience with a patient experiencing a near-fatal, acute reaction following the oral administration of iodoalphionic acid, preparatory to cholecystography, was considered noteworthy and therefore prompted the reporting of this case in order to point out this apparently rare but potentially serious manifestation of hypersensitivity in a procedure hitherto considered innocuous.

CASE REPORT

K. S., a 43-year-old clerk, was admitted to this hospital on Oct. 24, 1955. For the past eleven years he had complained of recurrent attacks of postprandial epigastric discomfort, accompanied by nausea and occasional vomiting. Investigation of these complaints in the

From the Medical Service, Veterans Administration Hospital, Wilkes-Barre, Pennsylvania. Received for publication April 3, 1956.

*Attending physician (Allergy).

**Chief of Medical Service.

past had included diagnostic x-ray procedures, including a gastrointestinal x-ray series, cholecystogram three years previously, and an intravenous pyelogram seven years previously, with normal roentgenographic findings. He could recall no untoward reactions to any of these procedures. Because of a recent exacerbation of symptoms, his physician decided to repeat the gall bladder studies. As directed, on Oct. 24, 1955, at 6:00 P.M. he took two tablets of iodoalphionic acid and continued to take two tablets every five minutes until he had ingested a total of twelve tablets. Two hours later, at approximately 8:00 P.M., he began to complain of generalized pruritus soon accompanied by the appearance of giant urticarial wheals which rapidly progressed until almost the entire skin was involved. At 9:30 P.M., he reported to the hospital complaining of the skin lesions and associated marked pruritus. Shortly after his arrival at the hospital, while being examined, the patient suddenly collapsed and became comatose. The blood pressure was unobtainable and marked respiratory distress with inspiratory stridor developed. Emergency treatment was instituted, which included adrenalin 1-1,000, 0.5 ml. subcutaneously; diphenhydramine hydrochloride, 10 mg. intramuscularly; and hydrocortisone, 100 mg. in 500 ml. of 5 per cent glucose, intravenously. With this therapy, the blood pressure gradually returned to normal levels and the respiratory difficulty subsided. The urticaria disappeared during the next twelve hours. Treatment with hydrocortisone intramuscularly and later orally was continued for the next two days, during which time there was no recurrence of symptoms. A gall bladder x-ray on the day after admission revealed a normally functioning organ thus indicating absorption and concentration of the media.

A complete physical examination later revealed no abnormal physical findings and all laboratory tests, chest x-rays, and electrocardiographic tracings were within normal limits.

A review of the past history referable to allergic manifestations revealed that three years previously he had experienced a penicillin reaction manifested by symptoms of urticaria that persisted for only three or four days. Subsequently, he had taken courses of penicillin orally without the appearance of similar symptoms or other untoward effects. An allergy survey failed to reveal any evidence of associated atopic manifestations. There was no history of symptoms of asthma, allergic rhinitis, atopic dermatitis, migraine, urticaria, or angioedema other than that associated with the transient drug reactions, food intolerances, or other associated allergic symptoms.

A routine survey of intracutaneous tests to common perennial inhalant, food, mold, and pollen allergens was negative. An attempt was made to detect circulating reagins against suspected iodide containing antigens by means of the Prausnitz-Küstner serum passive transfer technique. The patient's serum was transferred intracutaneously to multiple skin sites of normal recipients. After the suitable time period these recipient sites were challenged by the following methods: (1) scratch test with sodium iodide; (2) scratch test with iodoalphionic acid powder and N/10 sodium hydroxide; (3) oral administration of iodoalphionic acid; and (4) intracutaneous tests with serum of normal patients who had taken tablets of iodoalphionic acid orally three hours previously. Negative reactions were obtained following the first three testing procedures and, in the last instance, equally positive whealing reactions were obtained in both the passively transferred and normal control sites apparently due to the nonspecific whealing effects of the serum, even when diluted 1-100 in physiologic saline.

Continued observation and follow-up examinations of this patient have shown him to remain asymptomatic since the initial episode, taking no medication and avoiding all iodide-containing drugs and foods.

COMMENT

Iodide sensitivity through allergic mechanisms is a well-documented phenomenon and a discussion of this need not be entered into here. Though fortunately rare, anaphylactoid reactions of the type suffered by this patient have been reported in iodide-sensitive patients receiving contrast media by the intravenous route,[2, 4] apparently as a result of being immediately presented

with a high blood level of the offending antigen. It is therefore considered a highly unusual situation when this clinical picture presents itself in an otherwise nonatopic individual following the oral ingestion of an organic iodide compound with which only minor allergic reactions have been reported[6-8] after extensive use. The only other severe allergic reaction to iodoalphionic acid described has been that of a near-fatal attack of severe asthma in an iodide-sensitive patient reported by Sheldon and Lovell.[9]

Since this material is rapidly absorbed from the gastrointestinal tract into the blood stream, an anaphylactoid reaction of this type is entirely possible if the blood concentration should reach a critical level in a highly sensitive patient. This is in contrast to the analogous situation in penicillin sensitivity where the oral administration of penicillin, potentially capable of producing anaphylactic reactions, is considered a relatively safe procedure[10] even in sensitive individuals because of its slower rate of absorption. In this regard, it is also of interest to note that the relative infrequency of severe reactions following the intrabronchial installation of iodized oil in bronchography has been attributed to the stability of the chemical combination of the iodine and unsaturated fats resulting in little decomposition of the oil in the lung.[11]

It is of interest to point out that this patient had previous exposure to iodide-containing contrast media without any untoward reactions noted. An intravenous pyelogram had been done seven years before and a cholecystogram three years previous to this exposure and reaction to iodoalphionic acid. In all probability these previous exposures, though without reactions themselves, served as the sensitizing mechanisms, although one might suspect that the development of this high a degree of hypersensitivity would be preceded by some lesser allergic manifestations on previous exposures. It is entirely possible that the hypersensitivity existed specifically to iodoalphionic acid or some other radical of this compound rather than to the iodide portion since this could be neither proved nor disproved by available diagnostic procedures, skin tests, or other confirmatory data. The etiology of hypersensitivity to iodoalphionic acid in the production of this patient's anaphylactoid reaction can only be suspected and the diagnosis made only on the grounds of clinical association. The only other ingredients contained in these tablets were cornstarch and magnesium stearate[7] and allergy to these were excluded in this patient. The failure to demonstrate circulating reagins in the patient's serum does not imply that they did not exist since there is no definite knowledge of the exact offending antigen. One can only suspect that this may be iodine and/or iodoalphionic acid but the failure to demonstrate positive whealing reactions to these only demonstrates once again the failure of skin tests when dealing with suspected simple chemical antigens.[12]

Suspecting that the antigen might be iodine in haptenic combination with a serum protein, a test antigen of serum from a normal individual who had absorbed iodoalphionic acid into his blood stream from his gastrointestinal tract was used as a test antigen. However, the nonspecific irritating effects of the serum itself prevented its usefulness in the detection of reagins. In addition

to the limitations of all simple chemicals as skin test antigens,[12] iodoalphionic acid presents its own particular problems in this regard. This material, a crystalline powder, is insoluble in water or saline. It is partially soluble in benzene and chloroform; soluble in alcohol, ether, and in alkali carbonate, or hydroxide solutions.[7] These resulting solutions are unsuitable for intracutaneous injection or conjunctival instillation because of their nonspecific irritating properties, or high pH. The solubility of iodoalphionic acid in hydroxide may be taken advantage of by applying a paste of the powder in N/10 sodium hydroxide in scratch test procedures. Though the scratch test is generally a less sensitive technique than the intracutaneous test in eliciting sensitivity, it may be reliably employed even in Prausnitz-Küstner passive transfer tests.[13] Thus, the scratch test, though limited in sensitivity and of undetermined accuracy in this situation, may be the only method available for any future studies or attempts in screening patients potentially sensitive to the orally administered cholecystographic contrast media currently available.

SUMMARY

1. A case report is presented in which a nonatopic patient with no previous history of iodide sensitivity developed an anaphylactoid reaction characterized by urticaria, angioedema, dyspnea, loss of consciousness, and cardiovascular collapse following the oral administration of iodoalphionic acid, a cholecystographic contrast media.

2. Prompt treatment with adrenalin, parenteral antihistaminics, and adrenal corticosteroids resulted in complete recovery.

3. Attempts to demonstrate circulating reagins against iodide and iodoalphionic acid were unsuccessful.

Iodoalphionic acid (Priodax) in crystaline form was supplied by Dr. G. K. Hawkins of the Schering Corporation. His assistance in this study and case report is gratefully acknowledged.

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PYREXIA DUE TO ISONICOTINIC ACID HYDRAZIDE

JOHN J. WALSH, M.D.,* RICHARD H. LINN, M.D.,** AND VINCENT J. DERBES, M.D.,*** NEW ORLEANS, LA.

IN GENERAL, adverse reactions to isonicotinic acid hydrazide have been limited to involvement of the central and peripheral nervous systems. These include muscular twitching and irritability, peripheral neuritis, convulsions, and psychoses. Vague abdominal distress, nausea, diarrhea or, more commonly, constipation are the gastrointestinal symptoms encountered with the drug. Rarely, dermatitis or purpura has been noted.

Drug fever, so frequently a complication of other therapeutic agents, is not generally recognized as a manifestation of hypersensitivity to isonicotinic acid hydrazide. A recent report[1] of this complication was thought to be the first such case. While a review of the literature reveals similar complications reported at least one year prior to the above report,[2, 3] the occurrence of this complication is of sufficient rarity to warrant the present case report. (It should be noted that this rarity is probably only apparent and due to the paucity of cases reported rather than actual incidence.)

CASE REPORT

The patient, a 38-year-old seaman with no previous or family history of allergic diathesis, was initially hospitalized on Oct. 30, 1954, because of giant urticaria developing ten days after an injection of procaine penicillin. He had received the latter several times, without difficulty, in the distant past. Routine chest roentgenogram revealed moderately advanced pulmonary tuberculosis with cavitation. Tubercle bacilli were demonstrated on smear and culture of the sputum. On Nov. 14, 1954, chemotherapy in the form of isonicotinic acid hydrazide (INH), 100 mg. three times daily, and para-aminosalicylic acid, 4 Gm. thrice daily, was started. He had never received either drug previously. Nine days later the patient developed shaking chills, malaise, myalgia, and nausea. His temperature spiked to 101.2° F. Prior to this he had been afebrile and asymptomatic. Chemotherapy was discontinued on the following day, the patient becoming asymptomatic and afebrile within eighteen to twenty-four hours after discontinuation of INH and remaining so until medication was reinstituted.

On Nov. 27, 1954, the patient was again started on isonicotinic acid hydrazide, 100 mg. three times daily, since para-aminosalicylic acid was thought to be the offending agent. He remained symptom free and afebrile until Dec. 2, 1954, when he again developed malaise, myalgia, nausea, chills, and fever. Isonicotinic acid hydrazide was discontinued after the last dose of December 3, but the patient continued symptomatic and febrile (102 to 103 degrees) for approximately twenty-four hours.

On Dec. 16, 1954, he was given 100 mg. of isonicotinic acid hydrazide at noon and at 5 P.M. Within several hours he developed symptoms identical to those noted in the two previous episodes. Temperature approximated 102 degrees. These symptoms lasted for

From the Departments of Medicine, United States Public Health Service Hospital, New Orleans, Louisiana,* ** Tulane University School of Medicine,** *** and the Louisiana State University School of Medicine.*

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less than twenty-four hours and responded to symptomatic treatment, as had all previous episodes. There were no abnormal laboratory or x-ray findings attributable to any of the three reactions.

DISCUSSION

The nine-day incubation period in this patient is similar to that seen in other allergic, or presumed allergic, febrile conditions. Thus, of 1,493 cases of serum sickness collected by Longcope,[4] the incubation period was eight to nine days in one-third and ranged between six and ten days in 1,053 (70 per cent). Because of the widespread use of Nirvanol in the treatment of

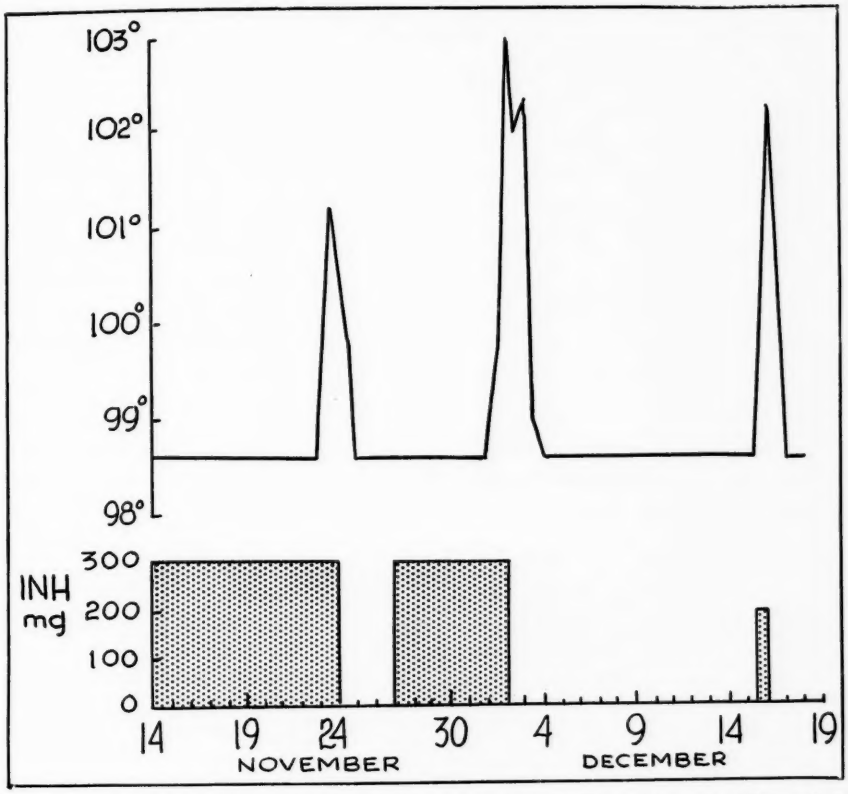

Fig. 1.—Progressive telescoping of incubation periods between ingestion of INH and febrile response (nine days, four days, and six hours, respectively).

Sydenham's chorea, numerous instances of Nirvanol sickness have been observed. This is a well-defined disease which invariably produces the same symptoms and signs with an almost constant incubation period. Fever, morbilliform, erythematous, or multiform eruptions, drowsiness, eosinophilia, and slight leukocytosis appear six to eight days after ingestion of the drug. These last three to six days and are followed by complete recovery. The regularity of the incubation period and the constant clinical course have led to the assumption that it is allergic in nature. But second courses, according to Madden,[5] rarely give rise to immediate reactions.

Yet another well-described condition has a similar incubation period. This is the formerly frequent erythema of the ninth day of Milian, a febrile exanthema which appears nine days after the first injection of neoarsphenamine. The five- to nineteen-day incubation period is quite constant; in the average case, it is seven or eight days. As a rule, one to three injections of the arsenical intervene between the first dose and the onset of the illness. Subsequent treatment with arsenicals within two weeks is followed by serious complications. If such therapy is postponed for a longer period, various forms of arsenical reactions result in about one-fourth of the instances, some of them being repeated bouts of typical erythema of the ninth day.

A series of papers report fever after numerous other drugs. In general the tenor of the various articles has been that fever, without other assignable cause, which disappeared on withdrawal of the drug may be taken to be allergic. This appears to beg the question. Other types of drug reaction which appear in only a certain number of persons, and which invariably have an incubation period, are known not to be on an allergic basis. Tachyphylaxis in general is such a phenomenon; hypokalemia after corticosteroids is another. Longcope may be quoted: "In spite of the circumstances that have led many to regard these intoxications as a form of allergy to one or another of these sulfonamide drugs, it has been almost impossible to bring proof of this by the use of conventional tests. Occasionally the patch test is positive but this is rare, and other specific reactions cannot be demonstrated. The situation is quite the same as that which exists in other forms of drug allergy."

Although subsequent work may furnish proof of the allergic nature of these febrile drug reactions, it seems accurate at this time to state that the mechanism of their production is unknown. Allergists thus share the common ignorance about the pathogenesis of fever; a recent editorial in the *American Journal of Medicine*[6] points out that, of the many different types of disease associated with fever (infections, neoplastic diseases, hemolytic crises, vascular accidents, and mechanical injuries) only in the case of neurogenic fever resulting from direct injury to the central nervous system is the origin of the febrile response clearly understood.

SUMMARY

On three occasions institution of isonicotinic acid hydrazide therapy resulted in a severe febrile reaction which subsided promptly with symptomatic care and discontinuation of the drug. Will each episode the untoward symptoms were more severe and the latent period shorter, indicating the development of increasing sensitivity. It is believed that pyrexial reactions to isonicotinic acid hydrazide are uncommon, but not rare, and that this case represents such an occurrence.

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American Academy of Allergy

PRESIDENT'S ADDRESS

STANLEY F. HAMPTON, M.D., ST. LOUIS, MO.

THE AMERICAN FOUNDATION FOR ALLERGIC DISEASES, THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, AND THE SECOND CONGRESS OF THE INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

FELLOW MEMBERS OF THE ACADEMY, WIVES, AND GUESTS: It is with a sincere feeling of humility, but also with pride, that I stand before you today as president of the American Academy of Allergy. I want to thank you for attending this luncheon, an annual event instituted in 1953 for a dual purpose, namely, to substitute for the annual formal banquet which was discontinued several years ago and to provide a place for the president each year to report to the membership, thereby relieving the annual business meeting of this burden.

In 1953 President Walter Burrage reviewed the history of the founding, in 1923, of the two parent societies and the development of the Academy since its birth in 1943. In 1954 President Ben Rappaport spoke to you on the then new American Foundation for Allergic Diseases and urged its support by every allergist in the country. Last year President John Sheldon, in an address entitled "Undergraduate Medical Education in Allergy," pointed out that ". . . instruction of the undergraduate medical student in allergic problems has lagged behind the organized presentation of other subjects in the field of medicine" and outlined a plan for undergraduate education in allergy from the freshman through the senior years of schooling. Today I would like to report to you on several activities concerning the Academy during this fiscal year.

This year the Academy has continued to prosper and fulfill its purpose, as laid down in its Constitution: "The object of the Academy shall be the advancement of the knowledge and practice of allergy, by discussion at meetings, by fostering the education of students and the public, by encouraging union and cooperation among those engaged in this field, and by promoting and stimulating research and study in allergy." I feel that we have carried out these objectives this year in a number of ways. We have continued the custom of preconvention postgraduate teaching and exchange of ideas. The membership of the Academy has cooperated to the fullest in submitting a large number of abstracts of original investigation to make the annual meeting's scientific

Presented at the twelfth annual meeting of the American Academy of Allergy, Feb. 6-8, 1956, St. Louis, Missouri.

program a good one. Furthermore, we were most fortunate in having Drs. Herman Eisen, Charles Janeway, Irving Kerlan, Carl Moore, and Sidney Raffel as our guest speakers.

There are three additional accomplishments this year that concerned the Academy either directly or indirectly.

First, the American Foundation for Allergic Diseases, after three years of organization activities, continued to develop through the untiring efforts and excellent leadership of its president, Dr. Horace Baldwin, and of the Foundation's Scientific and Educational Council, whose chairman is Dr. Robert A. Cooke. The Foundation, in December of 1955, established and announced its three-point national program of (1) fundamental research, with six distinct areas, (2) education and training of physicians in allergy, and (3) dissemination of information about allergy to the public, with a three-year budget of $1,100,000. I am sure that I express the feeling of every member of the Academy in wishing the Foundation Godspeed, but they will need your support.

Second, it is with great pleasure that I call to your attention the fact that, for the first time in the history of medicine, there has been established, within the framework of the National Institutes of Health, a National Institute of Allergy and Infectious Diseases. This took place only two or three weeks ago. To me, this probably is the greatest thing that has happened to allergy since von Pirquet coined the term in 1906, and it should be the steppingstone to finding the key (to borrow from Osler) to unlock the mystery of antigen-antibody mechanisms, autosensitization, histamine, collagen disease, drug reactions, and enzymes as they are related to common and uncommon allergic syndromes. This means that funds will be available for well-founded research. Let us, the allergists, strive to unlock these mysteries rather than have them unlocked by our colleagues in other fields of medicine. We have the honor and pleasure of having with us today Dr. Leonard Karel, Chief of the Extramural Programs of this new institute, who will speak to us on this subject.

Third, the second congress of the International Association of Allergology was held in Rio de Janeiro, Brazil, Nov. 6 to 12, 1955. The Academy, as one of the component societies of the I. A. A., can be proud of its participation and assistance in this congress. The Rio Committee of the Academy, composed of Drs. Sam Feinberg, John Sheldon, Carl Arbesman, Max Samter, and myself, with Dr. Howard Osgood as chairman and Dr. Francis Rackemann as honorary member, cooperated with the Program and Finance Committees of the I. A. A. in helping to make the meeting a successful one.

The Finance Committee of the I. A. A., composed of Academy members Arbesman, Brown, Feinberg, Wittich, and myself, sought and secured funds to help defray expenses of guest speakers to the meeting. Those contributing were the Lasdon Foundation and several pharmaceutical companies—Burroughs Wellcome, Ciba, Hoffmann-La Roche, Hollister-Stier, Parke-Davis, Pfizer, Schering, Travenol, and Westwood.

Most of those attending the meeting arrived in Rio on Friday and Saturday, November 4 and 5, depending upon the airline schedules of arrival times of planes from various countries of the world. On Sunday morning there

was a great outflux en masse from the Rio hotels and everyone proceeded by chartered buses and automobiles to the site of the congress, Petropolis, a beautiful resort mountain town about 40 miles out of and 2,500 feet above Rio. I attended the congress as your delegate. About thirty members of the Academy, exclusive of our foreign members, attended the meeting. The total attendance was approximately 350 from thirty different countries of the world. The congress was held at the Quitandinha, a large and palatial hotel.

The program started on Sunday afternoon, November 6, with addresses of welcome by Brazilian government representatives and local arrangements chairmen, including Drs. F. E. Robello (president of the Brazilian Allergy Society) and N. Brum Negreiros and U. Fabiano Alves, chairman and secretary of the Local Arrangement and Organizational Committees. The presidential address was given by Dr. Fred Wittich, fellow of the American Academy of Allergy. The four honorary guest speakers—Drs. Robert A. Cooke of the United States, C. Jiminez-Diaz of Spain, M. Rocha e Silva of Brazil, and Sir Henry Dale of England—are all honorary fellows of the Academy. These distinguished allergists (Dr. Dale was not present but supplied printed copies of his essay) presented scientific papers of outstanding merit on various phases of allergy in completing the program of the first day of the congress. For six days thereafter the scientific program was comprised of simultaneously conducted sectional meetings and symposia on dermatologic allergy, histamine, immunology and allergy, drug allergy, allergy and hormones, the asthmatic patient, and miscellaneous phases of allergy, including tuberculosis and leprosy. A total of 151 papers were presented.

Whereas translation was not provided during the first two and one-half days of the congress, translation in Portuguese, Spanish, French, and English was conducted most satisfactorily during the remaining sessions of the meeting, the reception being accomplished by means of earphones for each member of the audience and central interpreters for each of the four languages.

Twenty-two delegates, representing twenty-two national allergy societies from twenty different countries, were present at the business sessions (House of Delegates meeting). All but three of the twenty-eight component societies of the Association were represented, either by a delegate in person or by proxy, of which there were only three. It was decided that the third congress would be held in Paris, France, in the fall of 1958, probably the latter part of October. The following were elected as officers and members of the Executive Committee: *President* (previously elected in 1951 as president-elect), Samuel M. Feinberg (U. S. A.); *President-Elect,* Bernard Halpern (France); *Secretary-General,* Jose Quintero Fossas (Cuba); *Treasurer,* Egon Bruun (Denmark); *First Vice-President,* Guido Ruiz-Moreno (Argentina); *Second Vice-President,* Bram Rose (Canada); *Third Vice-President,* Umberto Serafini (Italy); *Members-at-Large,* David Williams (England), Ethan A. Brown (U. S. A.), Paulo Dias de Costa (Brazil), and Howard Osgood (U. S. A.). All are members of the American Academy of Allergy.

The gracious hospitality of the Brazilians and other South American hosts was appreciated by the North Americans. Even a one-day civil war or revolu-

tion was provided for us, apparently brought about by a slight misunderstanding between the Brazilian Army and Navy. This created a small disturbance among the congress personnel, to say the least. It took place on Friday morning. Thursday afternoon had been a "free" afternoon, with no scientific program, so that some were in Rio proper, where the guns were fired, preparing to return to Petropolis and the congress that morning. Those at Petropolis at the time soon received word of the fracas and I am afraid that the attendance at the scientific sessions on that day and the next was somewhat affected by this event. Restriction were imposed in Rio for one day only and by the time the congress was over, all was quiet on the Rio front, with activities returning to normal.

The automobile driving and traffic customs in Brazil appear to be quite different from those in the United States. It seems that the one who arrives at a point first, such as an intersection, has the right of way; a pedestrian is at fault if he is struck by a vehicle; and, if one can leave the scene of an accident and remain in hiding for twenty-four hours, he is relieved of all liability. I want to congratulate each member of the Academy who went to Rio, drove in automobiles and taxicabs, crossed streets on foot, and still returned home unscratched.

Following the congress, some of us had the pleasure of visiting medical schools and hospitals and discussing Allergy with South American physicians in Rio and São Paulo, Brazil; Montevideo, Uraguay; Buenos Aires, Argentina; Santiago, Chile; and Lima, Peru.

Do not think that we are alone as pioneers in medicine on this continent. The practice and teaching of medicine in South America, in many instances, predates that in the United States. Aristides A. Moll[1] in his book entitled *Aesculapius in Latin America,* states: "Fully 160 years before the first hospital in the early American colonies opened its doors on Long Island, New York, in 1663, the Spaniards were already coping with the same problem farther south." In Brazil the first hospital, called Mercy Hospital, was built about 1543 at the site of the present coffee emporium in the city of Santos.[1] There is, at present, a hospital in Rio that was built and started operating in 1582.

The first medical school in South America was established in Lima, Peru, in 1621. The first school of medicine in the United States was founded at Harvard University in 1782,[2] and not many years later schools were founded in Buenos Aires (in 1801) and Rio de Janeiro (in 1808).[1] The currently operating Faculdade National de Medicina Universidade do Brasil was founded in 1821. The present Academy of Medicine of Rio de Janeiro was founded in 1829, while the New York Academy of Medicine was established in 1847 and the St. Louis Medical Society in 1837.[3]

There is a type of socialized medicine practiced in most of the South American countries. In Brazil there is a compulsory prepayment payroll deduction health insurance program controlled and regulated by the federal government. This limits the private practice of medicine to a small group

of self-employed and professional personnel. There are numerous government-controlled hospitals to serve the patient and there are some private hospitals. Hospitalization in a private hospital, I am told, is very costly.

Most medical schools are sponsored, in South America, by the federal or state governments and are free to the student. Private medical schools exist but are very expensive. Nevertheless, it is said that basic research is handicapped by a shortage of financial support.

Several South American countries, including Brazil, Argentina, Chile, and Peru, have national allergy societies. It was my impression that the South American doctors are most interested in allergy and are ever looking for opportunities for better education, research, and clinical service to the patient, just as we are doing here. Let us foster the continued good neighbor policy with our South American colleagues, and with allergists of all nations. It was, indeed, an honor and a pleasure to be your delegate to the second congress of the International Association of Allergology, to get acquainted with and to exchange ideas with physicians interested in allergy from countries all over the world. Let me urge you to attend the third congress in Paris, France, in 1958.

I will have a few more words to say at the business meeting this afternoon, at which time I will acknowledge the valuable help given me by so many of you during this fiscal year. At this time, however, I want to express my appreciation for their indulgence to the staff of the Washington University Allergy Clinic; to my research associate, Miss Mary Johnson; to my associate in practice, Dr. Margaret Chieffi, and my office staff; and, most of all, to my wife for her patience, tolerance, and understanding during the past twelve months.

In closing, I would like to remind you that 1956 is a milestone in the history of allergy, the word *allergy* being 50 years old this year. Furthermore, it is the fiftieth anniversary of this country's Food and Drug Act, of which Dr. Kerlan will speak to us during this convention. May I urge you to make 1956 a big year for the Academy and for allergy, and to keep the welfare of the Academy close to your hearts. Let us all conduct ourselves in dealing with the public, in our practice, teaching, and research with the proper integrity and dignity so that not only will we be proud to be Academy members but also that the Academy will be proud of its membership.

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Obituary

ANDREW B. PAUL

ANDREW B. PAUL died on June 19, 1956, at Scardale, New York, after suffering a sudden heart attack. He was 55 years old.

Dr. Paul was a graduate of Budapest University. He was a staff member of the Manhattan Eye, Ear and Throat and University Hospitals in New York. He was a member of the American Medical Association, the American Academy of Allergy, the Medical Society of New York State, the Medical Society of the County of New York, the American-Hungarian Medical Association, and the Cornell Club of New York. He was the author of several books and papers on allergies.

Announcements

Residency in Allergy, Ohio State University Health Center

A fully accredited one-year residency in allergy is open to those who have had an internship and two years' residency in medicine. Clinical and private, adult and children, in- and outpatient services are available.

For further details, write: John H. Mitchell, M.D., 1625 Perry St., Columbus, Ohio.

International Association of Allergology

The third congress of the International Association of Allergology, under the presidency of Dr. Samuel M. Feinberg of Chicago, will take place at the Medical School in Paris, Oct. 26 to Nov. 1, 1958. The program will be composed of symposia and section meetings on clinical and immunologic phases of allergy. Facilities for scientific and commercial exhibits will be available. The Congress Organizing Committee is headed by Dr. Bernard N. Halpern, chairman, and Dr. André Holzer, secretary. Professor Pasteur Vallery-Radot is honorary president. For information, address the following:

For local (congress) details: Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris VII°, France.

For general information, program details, etc.: Dr. José Quintero Fossas, Secretary General, Paseo 313, Vedado, Havana, Cuba or Dr. Samuel M. Feinberg, President, 303 E. Chicago Ave., Chicago 11, Illinois.

Book Review

Histamine—A Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme and C. M. O'Connor. Boston, Little, Brown and Company, 1956. 472 pages. Price, $9.00.

This book contains papers and discussions presented at two symposia, jointly sponsored by the Ciba Foundation, the Physiological Society, and the British Pharmacological Society, held in April, 1955. Both were attended by outstanding authorities on histamine from all parts of the world. The first meeting, held at the Wellcome Foundation, consisted of a large number of short papers covering all biologic aspects of histamine. The second meeting, at the Ciba Foundation, consisted of a relatively few papers on the origin, fate, localization, and release of histamine in the body, together with informal discussions of them by the eminent scientists present. Most of the principal aspects of the subject are included in both symposia, giving a thorough coverage with divergent opinions on many unproved points.

Few fields of physiology are the subject of more active research at present time than that of histamine. While many points are still unsettled, the volume of careful study recently completed suggests that further progress will be more rapid, with the probability of important applications to medicine and particularly the field of allergy. This book is the most complete summary of the present status of the subject, and is highly recommended for all who are concerned.

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